Title

Noninvasive profiling of sweat-derived lipid mediators for cutaneous research

Journal

Skin Research and Technology, 25(1)

ISSN

0909-752X

Authors

Agrawal, Karan
Sivamani, Raja K
Newman, John W

Publication Date

2019

DOI

10.1111/srt.12617

Peer reviewed

HHS Public Access

Author manuscript

Skin Res Technol. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Skin Res Technol. 2019 January ; 25(1): 3–11. doi:10.1111/srt.12617.

Non-Invasive Profiling of Sweat-derived Lipid Mediators for Cutaneous Research

DR Karan Agrawal[1,2], **Raja K Sivamani**[3,4], and **John W. Newman**[1,2,5]

[1]Department of Nutrition, University of California-Davis, Davis, CA, USA

[2]West Coast Metabolomics Center, Genome Center, Davis, CA, USA

[3]Department of Dermatology, University of California-Davis Medical Center, Sacramento, CA, USA

[4]Department of Biological Sciences, California State University-Sacramento, Sacramento, CA, USA

[5]United States Department of Agriculture, Agricultural Research Service, Western Human Nutrition Research Center, Davis, CA, USA

Abstract

Background and Objective—Recent increases in the use of non-invasive matrices for biomedical analysis has led to interest in the evaluation of sweat for both clinical and research applications. However, despite being one of the two main cutaneous secretions, until very recently, only one study actually analyzed sweat in the context of cutaneous disease. This review attempts to make the case for increased use of sweat in cutaneous research, and discusses lipid mediators as potential analytical targets in sweat.

Methods—Sweat composition and its relationship with the skin and systemic circulation are discussed, as are practical considerations for sweat sampling and analysis. Previous analyses of lipid mediators in skin biopsies are provided to show that lipid mediators can regulate cutaneous processes and disease pathways. Summaries of recent studies involving the analysis of sweat lipid mediators are provided to demonstrate the utility of sweat lipid mediator testing to support future cutaneous research studies.

Results—Sweat has the potential to reflect both local and systemic biochemical changes in response to disease or intervention, and two recent studies of sweat lipid mediators confirm this ability. Additionally, sweat lipid mediators appear to be temporally stable with individual variability comparable other matrices, suggesting these analytes could be useful biomarkers.

Conclusions—Sweat metabolites may be capable of reporting changes in cutaneous biochemical pathways, thereby providing insight into the immunomodulatory biochemistry of the skin. Lipid mediator analysis of sweat appears to be a non-invasive approach that could enhance existing cutaneous research and diagnostic methodologies.

Corresponding Author: John W. Newman, PhD, 430 W Health Sciences Drive, Davis, CA 95616, USA, Phone: +1 (530) 752-1009, john.newman@ars.usda.gov.

Keywords

Oxygenated Lipids; Endocannabinoids; Ceramides; Sphingolipids; Skin; Metabolic Profiling; Non-invasive Sampling

Introduction

Sweat is a complex hypotonic biofluid produced by the eccrine, apocrine and apoeccrine glands of the skin, and along with sebum, is one of the two major cutaneous secretions. Sweat's physiological role in heat dissipation is well known, but early knowledge of its composition was traditionally limited to water, electrolytes, urea, lactate, amino acids, metals and xenobiotics (1). This knowledge has resulted in sweat being historically used for the diagnosis of cystic fibrosis, since the disease alters the ionic composition of sweat (2), and for forensic analysis to evaluate controlled substance use (3). With recent advances in analytical as well as sweat sampling technology, the composition of sweat has been further characterized, and it is now known to contain a much larger spectrum of molecules, including proteins, carbohydrates, organic acids, lipids, and lipid-derived metabolites (4–8). Correspondingly, the potential applications of sweat for diagnostic purposes have increased, including speculations that the sweat proteome may be useful for the diagnosis of infections, and psychiatric and neoplastic diseases (7, 9, 10). It should be noted that the vast majority of these studies characterized the composition of eccrine sweat, which is produced from sweat glands located throughout the body. Apocrine and apoeccrine sweat glands located in the axillary and genital regions of the body have a distinct secretory mechanism from eccrine sweat glands, and apocrine and apoeccrine sweat are less well characterized compared to eccrine sweat. Therefore, (eccrine) sweat might offer access to a potentially valuable and noninvasive biological sample that could help improve subject compliance in pharmacokinetic and biomedical studies, as has been demonstrated with other non-invasive matrices such as hair, saliva and tears (11).

To the best of our knowledge, only one example exists that examines sweat composition in the context of cutaneous disease, a study that examined sweat prostaglandin (PG) E2 levels in individuals with atopic dermatitis, psoriasis or hyperhidrosis compared to controls (12). While no overall differences were found between the subjects with the various diseases and controls in the cited study, some subjects with each disease did show markedly higher concentrations of PGE2 compared to the average control, suggesting that there may in fact be some cutaneous diagnostic potential to sweat. Interestingly, no further work has been published that evaluates the diagnostic potential of sweat in cutaneous disease, which is particularly surprising given that sweat is one of the two main cutaneous secretions. Therefore, this mini-review focuses on the potential for sweat, particularly eccrine sweat, to be a novel tool in cutaneous research and diagnosis. Additional emphasis will be placed on lipid mediators as analytes of interest in demonstrating the utility of sweat in cutaneous research, particularly given the previous attempt at evaluating these compounds in sweat for this purpose.

Lipid Mediators and Their Association with Cutaneous Disease

Lipid mediators refer to derivatives of fatty acids that display biological activity and are capable of regulating a variety of processes, including inflammation, cell growth and differentiation, and vascular homeostasis (13). These mediators, which come in a variety of forms, are generally produced locally via biosynthetic pathways in response to extracellular stimuli and function similarly to local hormones or autacoids (13), however they may also have endocrine functions, as they can be released from tissues during triglyceride lipolysis (14), and are components of circulating lipoprotein particles (15). Common examples of lipid mediator classes include oxygenated lipids ("oxylipins"), which constitute a chemical superclass consisting of the cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) derived products of polyunsaturated fatty acids; endocannabinoids and endocannabinoid-like compounds such as monoacylglycerols (e.g. 2-archidonoylglycerol, 2-AG) and acylethanolamides (e.g. arachidonoylethanolamide or anandamide, AEA); and ceramides and sphingosines (collectively, "sphingolipids"). The formation and biological roles of these lipid mediator classes have been reviewed elsewhere and are beyond the scope of this manuscript (13, 16, 17). The abbreviations used to describe the oxylipins, endocannabinoids, sphingoid bases, and ceramides mentioned in this manuscript follow standard conventions in the field, and are described and expanded elsewhere (18, 19).

Within the context of the skin, the presence of lipid mediators has been documented in keratinocytes, fibroblasts, melanocytes and sebocytes, and these compounds have been shown to influence a variety of cutaneous processes including cell proliferation, T-cell activation, epidermal barrier function and sebum synthesis (16). These findings led to inquiries into the role of lipid mediators in cutaneous disease, starting with demonstrations that lipid mediators influence pathways known to be involved in particular diseases, and later by demonstrating changes in lipid mediator concentrations in individuals with a disease compared to controls. More recently, lipid mediators have been used as a basis of treatment in several cutaneous diseases, most notably the use of palmitoylethanolamide (PEA)-containing creams for the treatment of atopic dermatitis (20). Most of these associations have been reviewed in several recent publications (16, 20, 21), and examples of specific lipid mediators and the skin diseases they are associated with may be found in **Tables 1 and 2**. However, as can be seen in these tables, most of the cited studies tend to focus on a limited number of lipid mediator targets and/or a single class of lipid mediators. This prevents the identification of mediator pathway cross-talk and limits the scope of discovery in these studies.

The basis for lipid mediator cross-talk lies in the notion that all classes of lipid mediators originate from similar fatty acid precursors, alternate biosynthetic pathways contain mediators of similar physiology (e.g. anti-inflammatory effects of oxylipins and endocannabinoids), and the enzymes responsible for lipid mediator formation collectively exist within most common cell types and often compete for fatty acid substrates. Specific evidence of lipid mediator cross-talk can be found in the interconversion of lipid mediator classes, such as the conversion of 2-AG to PGE2 1-glycerol by COX-2 (22); or inhibition or enhancement of lipid mediator forming enzyme activity by other lipid mediators, such as the inhibition of COX-2 activity by 2-AG or modulation of phospholipase A2 and COX-2

activity by sphingolipids (23, 24). While previously available technology did not permit simultaneous analysis of multiple lipid mediator classes, more recent advances allow (for example) the analysis of oxylipins, endocannabinoids and ceramides from a single sample extract (18, 25). These advances should be taken advantage of in future studies that seek to examine the lipid mediator profile of a cutaneous disease, particularly as often inhibition of one lipid mediator may lead to downstream effects on other lipid mediator classes relevant to that disease, which may not be readily detected if only a single lipid mediator class is analyzed.

The Case for using Sweat (Lipid Mediators) in Cutaneous Research

The involvement of lipid mediators in skin disease has long been established, and several promising therapeutic targets have been identified for diseases such as psoriasis and atopic dermatitis (46, 50). The fact that lipid mediators have been found in multiple skin cell types and have been shown to modulate cutaneous processes makes them an even more attractive target for future research studies (16). Finally, given advances in analytical technology that permit simultaneous analysis of multiple lipid mediator classes, it is now possible to evaluate not only lipid mediator crosstalk, but also more comprehensively understand the impact a disease may have on cutaneous inflammation and immunomodulation, which may lead to the development of more targeted therapeutic interventions.

But where does sweat fit into this paradigm? As one of the two main cutaneous secretions, sweat offers promise as an informative non-invasive matrix in cutaneous research. It is well established that diseases such as cystic fibrosis genetically alter sweat composition, supporting its potential as a diagnostic matrix (2). Current understanding of sweat composition suggests that it is primarily an excretory biofluid, comprising secretions from both the local cutaneous environment by diffusion from surrounding skin cells, as well as the global systemic environment by diffusion from the capillary network surrounding the sweat gland coil (58). There is also some evidence that the epithelial cells of the sweat gland are also capable of synthesizing and secreting sweat components such as the endocannabinoids AEA and 2-AG (59). By contrast, skin lipid mediator profiles are only reflective of the local cutaneous environment, as lipid mediators are typically synthesized locally and function as local hormones or autacoids (13). Therefore, analysis of skin lipid mediators provides a relatively limited view of the effects of a particular disease, which could easily be expanded in a more non-invasive manner by the analysis of sweat.

From a sampling perspective, cutaneous research currently appears to be largely dependent on tissue biopsies or tape strips, both of which are invasive procedures and have potential to cause considerable discomfort to the subject. Tissue biopsies in particular are also not amenable to repeated temporal sampling, in part due to subject discomfort, but also because the affected or treated area is usually excised after the first biopsy. It has recently been suggested that invasive sampling procedures such as venipuncture can increase reluctance in subjects to participate or comply with biomedical study requirements, and that the use of non-invasive matrices such as saliva or sweat have improved compliance in pharmacokinetic studies (11). Given that sweat collection is generally a non-destructive and non-invasive process, it would appear to be suitable for repeated sampling and has the potential to

minimize subject discomfort, making it an excellent supplement to skin biopsies or tape strips.

Finally, -omics analysis of sweat is an emerging area that is currently of great interest to several research groups around the world (1, 60). A recent comprehensive review by Hussain *et al.* summarizes the last 10 years of sweat -omics analysis and shows that in addition to water, electrolytes and small molecules, sweat also contains proteins, carbohydrates, organic acids, and lipid-derived molecules to name a few classes of detected analytes (60). Each of these detected analytes represents a potential therapeutic target and/or previously unknown modulator of a skin disease. In fact, several of the proteins detected in sweat have demonstrated cutaneous immunomodulatory or pathogenic defense properties (61, 62). Therefore, continued exploration of sweat composition and its relationship to the skin should be encouraged, and efforts are currently underway to further our understanding of this highly promising biofluid.

Practical Considerations for Sweat Bioanalysis

Sweat Collection Methods—Until relatively recently, sweat has had limited application in the areas of metabolomic or lipidomic testing, in large part due to a lack of quantitative and reproducible methods for collecting sweat and their impact on the sweat metabolic profile (1, 60). Two recent reviews on sweat and its utility in metabolomics analysis provide overviews of the evolution of sweat collection technologies and discuss the advantages and disadvantages of these various methods (1, 60). It would be redundant to revisit these topics in this manuscript. Rather, it is worth considering the research questions desired to be answered by sweat analysis.

Methods that offer rapid and quantitative collection of liquid sweat such as the Macroduct® sweat collector are amenable for a wide range of studies since sweat collection occurs over a relatively short window (~ 30 min), and therefore it is possible to closely relate observed changes in sweat composition to the time since an intervention occurred. Since liquid sweat is collected, it is possible to measure the collection volume, which may offer a means to normalize amounts of detected analytes. The small size of these collection technologies also offers researchers the opportunity to choose the collection site, which can help minimize potential contamination by sebaceous secretions or even other types of sweat (e.g. apocrine or apoeccrine sweat), and direct sweat gland interrogations to areas of skin with varying levels of pathobiological intensity. However, these technologies are often expensive and usually require specially trained personnel to actually perform sampling.

By contrast, patch collection technologies such as PharmChek® are comparatively inexpensive, require no specialized training prior to use, and are also amenable to site-directed collection. However, collection windows for these technologies is usually on the order of hours to days, which makes it difficult to relate sweat composition to interventions not only due to the length of collection time, but also because the collected sample provides a cumulative view of metabolic changes throughout the collection period rather than a snapshot at the time of collection. Collected sweat usually evaporates from the patch which could lead to concentration of detected metabolites, making accurate quantitation of analytes difficult, as would be estimation of the volume of collected sweat (1). Such collection

technologies are perhaps most suitable for forensic or compliance testing where a positive or negative result is more important than an accurate quantitation.

Finally, collection technologies such as bags that encase a limb or whole body sweat collections are rarely used now, but require no specialized equipment or trained personnel. However, such collections are prone to contamination of the collected sweat by sebaceous secretions or the mixing of different sweat types, and are likely not suitable for metabolomics or bioanalytical studies.

Sweat Stimulation Methods—In order to collect a sufficient quantity of sweat for analysis, sweating must usually be stimulated, either by pharmacological methods (pilocarpine iontophoresis) or physiological methods (thermal induction or exercise) (1). Collection of sweat without stimulation is possible by the placement of an absorbent material such as a gauze pad on the skin surface, but this usually requires collection times of several hours or days to achieve a sufficient volume of sweat for analysis due to the relatively low rate of total body insensible sweating, e.g. 1–20 g/h at 25 °C and 60% relative humidity (63), whereas sweat collection following localized stimulation can usually be achieved within an hour (1). More detail on each sweat stimulation technique and its relative advantages and disadvantages is available elsewhere (60). It is worth noting that little work has been done to evaluate the impact of each of these collection techniques on overall comprehensive sweat composition. Based on the limited evidence in the literature, it does appear that sweat stimulation technique affects sweat composition, as both exercise and sauna increase interleukin (IL)-1 concentrations in sweat compared to pilocarpine iontophoresis, and sauna produces higher concentrations of sweat IL-1 compared to exercise (64). Similarly, thermal exposure and running generate different sweat electrolyte, creatinine and urea profiles (65). Therefore, care should be taken in selecting a sweat stimulation method, and results from studies involving different methods of sweat stimulation should be compared with caution. It is also worth considering the impact of age on sweat gland cellular functions (66).

An important consideration when stimulating and collecting sweat is the ambient environment. Temperature and humidity have both been demonstrated to influence sweating rates (67), and it is important to strictly control these parameters for all subjects in a given study no matter what sweat stimulation technique is used. Specific sweat stimulation techniques also have their own factors that require careful control. For example, if pilocarpine iontophoresis is the method of choice, it is important to control the dose of pilocarpine, the intensity of the current and the duration of stimulation. With exercise-induced sweating, it is important to control not only the duration of exercise, but also its intensity, as often the intensity of exercise can affect metabolism and therefore metabolic content (68). Heart rate and oxygen consumption have been previously shown to be excellent predictors of exercise intensity (69, 70), and at least one of these parameters should be monitored for all studies using exercise as a means of sweat stimulation. Carefully monitoring and regulating all of these parameters will result in a more uniform and therefore reproducible study.

Collection Sites—Most studies tend to sample sweat from the volar forearm, likely because it contains a low density of sebaceous glands, which minimizes the contamination of collected sweat by sebum (71). It is also relatively hairless, sun-protected, and relatively easy to access, which ensures minimal discomfort to subjects. Other anatomical sites such as the chest, abdomen, forehead or upper arm exemplify some of these characteristics as well, and in some cases, have a higher density of sweat glands and/or higher sweating rates compared to the volar forearm (72). Yet, these sites are not as frequently sampled for sweat. Possible reasons for this include the forehead being rich in sebaceous glands (73), and therefore any collected sweat likely being compromised by sebaceous secretions; the abdomen and upper arm not being as convenient to access, and also having lower sweating rates compared to the forearm (72); and sampling from the chest being potentially considered culturally invasive by some. There may be reasons to sample from these or other sites depending on the research question and/or location of lesions. It is thus worth considering the impact of collection site on sweat composition.

As with effects of different stimulation techniques on sweat composition, there are limited studies published that examine the impact of collection site. At first glance it would appear that collection site can affect sweat composition, as the ratio of IL-1α to IL-1β appears to change depending on whether the palmar/plantar surface or torso is sampled (64). However, sweat sodium and potassium concentrations appear unaffected by sampling from the forearm, back, chest, forehead or thigh (73). Therefore, it may be worth evaluating the impact of collection site on analytes of interest, particularly if comparisons are to be made with results published based on samples from a different anatomical location.

Normalization of Sweat Metabolite Concentrations—In order to obtain accurate and precise results from any analytical study, normalization of obtained results is a critical step (74). Results are frequently normalized to sample volume, and such an approach is appropriate where the sample matrix is homeostatically regulated, as is the case in blood and cerebrospinal fluid (74). On the other hand, matrices such as urine are not considered homeostatically regulated as volume-normalized analyte concentrations can vary significantly, even in the same individual, depending on factors such as hydration status and diet at the time of sampling (74). Creatinine is frequently used to normalize urine analyte concentrations, as it is assumed that creatinine concentration, which is produced at a constant rate from muscle tissue, provides a measure of the volume of blood filtered, and thus is reflective of urine diluteness (75). However, this approach is not always successful, particularly in cases of individuals with acute or chronic kidney diseases (76).

Sweat can also be considered a non-homeostatically regulated matrix, as sweat volume and rate are influenced by ambient temperature and humidity, and possibly by subject hydration status and blood flow to the sweat gland (67, 77). In an effort to normalize sweat analyte concentrations, particularly for patch-based sweat collection systems where it is difficult to quantify collection volume, Appenzeller *et al.* proposed the use of sweat sodium concentration as a normalizing factor (78). Such an approach can be confounded by diseases that affect sweat electrolyte content such as cystic fibrosis and adrenal insufficiency, and can be influenced to a lesser degree by individual diets (particularly sodium intake) (79, 80). To date, few studies that have attempted to normalize sweat analyte concentrations using

detected sweat electrolyte levels (81, 82). Chemical isotope labelling of sweat patches has been proposed as an alternative normalization strategy (83), and it may also be possible to normalize to the sample volume if a liquid sweat sample can be collected and the entire sample is analyzed (18). Sample normalization for sweat remains an area to be fully characterized in order to more develop standardized quantitative approaches.

Biological Relevance of Sweat Metabolite Profiles—The prevailing hypothesis for sweat composition is that as a predominantly excretory matrix, sweat is reflective of a combination of plasma filtration, sweat gland epithelial cell secretion, and in all likelihood, the influence of the surrounding cutaneous tissue mediators on the cells of the sweat gland (58). Most of the evidence for this hypothesis comes from drug delivery studies, as ketoconazole has been shown to rapidly partition from the bloodstream to eccrine sweat following oral consumption (84), whereas theophylline has been demonstrated to migrate transdermally to the skin surface where it can be amalgamated into sweat (85). It is critical to understand the sources of the detected metabolites in sweat so that obtained results may be put into the appropriate pathobiological contexts. This is particularly relevant in the area of lipid mediators, which are generally thought to be produced locally via biosynthetic pathways in response to extracellular stimuli and function similarly to local hormones or autacoids. It follows that any interpretations of lipid mediator concentration changes needs to be made in the context of the matrix of origin (13). There is also now evidence that cells of the sweat gland are capable of synthesizing some of the analytes detected in sweat (59), strengthening the argument that sweat merely reflects a modified plasma filtrate. Unfortunately, the source of most non-electrolyte analytes detected in sweat has not been well characterized at this time, and further studies need to be conducted to understand this critical aspect of sweat composition.

Current Status of Sweat Lipid Mediator Analysis and it's Applicability in Cutaneous Research

Since the initial publication in 1974 describing the presence of PGE2 in sweat by Forstrom *et al.* (12), we have been unable to find any subsequent characterizations of lipid mediators in sweat. We did however find mention that cells derived from the NCL-SG3 human sweat gland epithelial cell line are capable of *de novo* synthesis of AEA and 2-AG (59), which potentially adds another dimension to the characterization of the sources of sweat lipid mediators that was discussed in the previous section.

In an effort to more comprehensively characterize the sweat lipid mediator profile and understand its utility in cutaneous research, we recently attempted study in which we assayed eccrine sweat collected from the volar forearm of individuals with and without atopic dermatitis for over 150 lipid mediators to find differences between the groups (18). Fifty-eight lipid mediators were quantified in the collected sweat, including polyunsaturated fatty acid-derived alcohols, diols, epoxides and ketones; prostaglandins; nitrolipids; endocannabinoids; ceramides; and sphingosines, and the sweat of individuals with atopic dermatitis was shown to contain increased concentrations of [NS] and [NdS] ceramides compared to controls (18). Individuals with atopic dermatitis were sampled from a non-lesional site when they were in an unflared state, suggesting that sweat lipid mediator

profiling may provide an opportunity for preclinical diagnostic testing of atopic dermatitis. Further characterization of the sweat lipid mediator using more sensitive mass spectrometric technology increased the number of quantified sweat lipid mediators to 70 (19), suggesting that as analytical technology improves, so will our understanding of the sweat lipid mediator profile.

More recently, we evaluated the impact of different sampling techniques on the sweat lipid mediator profile, as well as the temporal stability of sweat lipid mediators, and were able to show that while exercise- and pilocarpine-induced sweat demonstrate different lipid mediator profiles, sampling location (volar forearm, anterior distal thigh or lower back) does not appear to affect sweat lipid mediator composition (19). Furthermore, sweat lipid mediators were shown to be temporally stable across the three-week duration of the study, and inter- and intra-individual variability were consistent with those observed in other matrices such as skin or plasma (19). While this study begins to alleviate some of the concerns described in the previous section, more work remains to be done on the stability and variability of sweat lipid mediators, particularly with respect to other methods of sweat stimulation such as thermal or emotional induction, as well as other anatomical sites such as the forehead, chest or upper arm.

Finally, we recently completed a study that evaluated the likelihood of the systemic circulation as a source of sweat lipid mediators, since the origins of the lipid mediators can help provide appropriate biological context for observed lipid mediator changes due to disease or therapeutic intervention (86). Sweat and plasma were collected from healthy individuals immediately prior to and at three times after ingestion of a 400-mg oral dose of ibuprofen (86). No correlations were observed between plasma and sweat lipid mediators at baseline (86), which suggests that systemic circulation is not a primary contributor to the sweat lipid mediator profile. Additionally, ibuprofen intake resulted in differentially affected lipid mediator profiles in the plasma and sweat (86), further supporting the notion that sweat lipid mediators are primarily derived from sources other than the systemic circulation. These findings shift the focus to skin or sweat gland epithelial cells as other potential sources of sweat lipid mediators, and add support to the idea that sweat primarily reflects cutaneous biochemical changes.

Conclusions

Throughout this piece, we have attempted to make the case for the use of sweat as a non-invasive matrix to support cutaneous research, particularly as sweat is one of the main secretions of the skin. It is hoped that readers will now appreciate that there is more to the composition of sweat than just water and electrolytes, and that metabolites present in sweat may in fact be capable of reporting changes in cutaneous biochemical pathways following pharmacological or physiological intervention, thereby providing novel insight into the immunomodulatory biochemistry of the skin. It is also hoped that this piece will inspire future studies into the composition of sweat and its utility as a biological matrix. We have only begun to scratch the surface of this new addition to cutaneous research, and there is much left to discover about this biofluid.

Acknowledgments

Funding

This work was supported by the National Institutes of General Medical Sciences [Grant No. T32-GM008799] (K.A.). Additional support was provided by the National Institutes of Diabetes and Digestive and Kidney Diseases [Grant No. U24DK097154–01] (J.W.N.), and the United States Department of Agriculture [Project No. 2032–51530-022–00D] (J.W.N.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIGMS, NIH or USDA. The USDA is an equal opportunity provider and employer.

References

1. Mena-Bravo A, Luque de Castro MD. Sweat: a sample with limited present applications and promising future in metabolomics. J Pharm Biomed 2014;90:139–147.
2. Gibson LE, Cooke RE. A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. Pediatrics 1959;23:545–549. [PubMed: 13633369]
3. De Giovanni N, Fucci N. The current status of sweat testing for drugs of abuse: a review. Curr Med Chem 2013;20:545–561. [PubMed: 23244520]
4. Harker M, Coulson H, Fairweather I, Taylor D, Daykin CA. Study of metabolite composition of eccrine sweat from healthy male and female human subjects by 1H NMR spectroscopy. Metabolomics 2006;2:105–112.
5. Kutyshenko VP, Molchanov M, Beskaravayny P, Uversky VN, Timchenko MA. Analyzing and mapping sweat metabolomics by high-resolution NMR spectroscopy. PLoS One 2011;6:e28824. [PubMed: 22194922]
6. Calderon-Santiago M, Priego-Capote F, Jurado-Gamez B, Luque de Castro MD. Optimization study for metabolomics analysis of human sweat by liquid chromatography-tandem mass spectrometry in high resolution mode. J Chromatogr A 2014;1333:70–78. [PubMed: 24529403]
7. Calderon-Santiago M, Priego-Capote F, Turck N, et al. Human sweat metabolomics for lung cancer screening. Anal Bioanal Chem 2015;407:5381–5392. [PubMed: 25935675]
8. Delgado-Povedano MM, Calderón-Santiago M, Priego-Capote F, Luque de Castro MD. Development of a method for enhancing metabolomics coverage of human sweat by gas chromatography-mass spectrometry in high resolution mode. Anal Chim Acta 2016;905:115–125. [PubMed: 26755145]
9. Raiszadeh MM, Ross MM, Russo PS, et al. Proteomic analysis of eccrine sweat: implications for the discovery of schizophrenia biomarker proteins. J Proteome Res 2012;11:2127–2139. [PubMed: 22256890]
10. Adewole OO, Erhabor GE, Adewole TO, et al. Proteomic profiling of eccrine sweat reveals its potential as a diagnostic biofluid for active tuberculosis. Proteomics Clin Appl 2016;10:547–553. [PubMed: 26948146]
11. Raju KS, Taneja I, Singh SP, Wahajuddin. Utility of noninvasive biomatrices in pharmacokinetic studies. Biomed Chromatogr 2013;27:1354–1366. [PubMed: 23939915]
12. Forstrom L, Goldyne ME, Winkelmann RK. Prostaglandin activity in human eccrine sweat. Prostaglandins 1974;7:459–464. [PubMed: 4415343]
13. Murakami M. Lipid mediators in life science. Exp Anim 2011;60:7–20. [PubMed: 21325748]
14. Schreiber R, Zechner R. Lipolysis meets inflammation: arachidonic acid mobilization from fat. J Lipid Res 2014;55:2447–2449. [PubMed: 25332433]
15. Shearer GC, Newman JW. Lipoprotein lipase releases esterified oxylipins from very low-density lipoproteins. Prostaglandins Leukot Essent Fatty Acids 2008;79:215–222. [PubMed: 19042114]
16. Kendall AC, Nicolaou A. Bioactive lipid mediators in skin inflammation and immunity. Prog Lipid Res 2013;52:141–164. [PubMed: 23124022]
17. Rabionet M, Gorgas K, Sandhoff R. Ceramide synthesis in the epidermis. Biochim Biophys Acta 2014;1841:422–434. [PubMed: 23988654]

18. Agrawal K, Hassoun LA, Foolad N, Pedersen TL, Sivamani RK, Newman JW. Sweat lipid mediator profiling: a noninvasive approach for cutaneous research. J Lipid Res 2017;58:188–195. [PubMed: 27875258]
19. Agrawal K, Waller JD, Pedersen TL, Newman JW. Effects of stimulation technique, anatomical region, and time on human sweat lipid mediator profiles. Prostaglandins Other Lipid Mediat 2018;134:84–92. [PubMed: 28942325]
20. Trusler AR, Clark AK, Sivamani RK, Shi VY. The endocannabinoid system and its role in eczematous dermatoses. Dermatitis 2017;28:22–32. [PubMed: 28098721]
21. Bíró T, Tóth BI, Haskó G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. Trends Pharmacol Sci;30:411–420. [PubMed: 19608284]
22. Kozak KR, Crews BC, Morrow JD, et al. Metabolism of the endocannabinoids, 2-arachidonylglycerol and anandamide, into prostaglandin, thromboxane, and prostacyclin glycerol esters and ethanolamides. J Biol Chem 2002;277:44877–44885. [PubMed: 12244105]
23. Nakamura H, Murayama T. Role of sphingolipids in arachidonic acid metabolism. J Pharmacol Sci 2014;124:307–312. [PubMed: 24599139]
24. Du H, Chen X, Zhang J, Chen C. Inhibition of COX-2 expression by endocannabinoid 2-arachidonoylglycerol is mediated via PPAR-γ. Br J Pharmacol 2011;163:1533–1549. [PubMed: 21501147]
25. Midtbø LK, Borkowska AG, Bernhard A, et al. Intake of farmed Atlantic salmon fed soybean oil increases hepatic levels of arachidonic acid-derived oxylipins and ceramides in mice. J Nutr Biochem 2015;26:585–595. [PubMed: 25776459]
26. Fogh K, Herlin T, Kragballe K. Eicosanoids in skin of patients with atopic dermatitis: prostaglandin E2 and leukotriene B4 are present in biologically active concentrations. J Allergy Clin Immunol 1989;83:450–455. [PubMed: 2537352]
27. Hua Z, Fei H, Mingming X. Evaluation and interference of serum and skin lesion levels of leukotrienes in patients with eczema. Prostaglandins Leukot Essent Fatty Acids 2006;75:51–55. [PubMed: 16757158]
28. Abramo F, Campora L, Albanese F, et al. Increased levels of palmitoylethanolamide and other bioactive lipid mediators and enhanced local mast cell proliferation in canine atopic dermatitis. BMC Vet Res 2014;10:21. [PubMed: 24423192]
29. Ishikawa J, Narita H, Kondo N, et al. Changes in the ceramide profile of atopic dermatitis patients. J Invest Dermatol 2010;130:2511–2514. [PubMed: 20574438]
30. Baumer W, Rossbach K, Mischke R, et al. Decreased concentration and enhanced metabolism of sphingosine-1-phosphate in lesional skin of dogs with atopic dermatitis: disturbed sphingosine-1-phosphate homeostasis in atopic dermatitis. J Invest Dermatol 2011;131:266–268. [PubMed: 20811395]
31. Arikawa J, Ishibashi M, Kawashima M, Takagi Y, Ichikawa Y, Imokawa G. Decreased levels of sphingosine, a natural antimicrobial agent, may be associated with vulnerability of the stratum corneum from patients with atopic dermatitis to colonization by Staphylococcus aureus. J Invest Dermatol 2002;119:433–439. [PubMed: 12190867]
32. Oka S, Wakui J, Ikeda S, et al. Involvement of the cannabinoid CB2 receptor and its endogenous ligand 2-arachidonoylglycerol in oxazolone-induced contact dermatitis in mice. J Immunol 2006;177:8796–8805. [PubMed: 17142782]
33. Karsak M, Gaffal E, Date R, et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. Science 2007;316:1494–1497. [PubMed: 17556587]
34. Petrosino S, Cristino L, Karsak M, et al. Protective role of palmitoylethanolamide in contact allergic dermatitis. Allergy 2010;65:698–711. [PubMed: 19909294]
35. Kendall AC, Pilkington SM, Sassano G, Rhodes LE, Nicolaou A. N-Acyl ethanolamide and eicosanoid involvement in irritant dermatitis. Br J Dermatol 2016;175:163–171. [PubMed: 26947140]
36. Hammarström S, Hamberg M, Samuelsson B, Duell EA, Stawiski M, Voorhees JJ. Increased concentrations of nonesterified arachidonic acid, 12L-hydroxy-5,8,10,14-eicosatetraenoic acid,

prostaglandin E2, and prostaglandin F2alpha in epidermis of psoriasis. Proc Natl Acad Sci 1975;72:5130–5134. [PubMed: 1061097]

37. Lew BL, Cho Y, Kim J, Sim WY, Kim NI. Ceramides and cell signaling molecules in psoriatic epidermis: reduced levels of ceramides, PKC-α, and JNK. J Korean Med Sci 2006;21:95–99. [PubMed: 16479073]
38. Kampfer H, Brautigam L, Geisslinger G, Pfeilschifter J, Frank S. Cyclooxygenase-1-coupled prostaglandin biosynthesis constitutes an essential prerequisite for skin repair. J Invest Dermatol 2003;120:880–890. [PubMed: 12713596]
39. Kozono S, Matsuyama T, Biwasa KK, et al. Involvement of the endocannabinoid system in periodontal healing. Biochem Biophys Res Comm 2010;394:928–933. [PubMed: 20233580]
40. Nicolaou A, Masoodi M, Gledhill K, et al. The eicosanoid response to high dose UVR exposure of individuals prone and resistant to sunburn. Photochem Photobiol Sci 2012;11:371–380. [PubMed: 22173231]
41. Yan Y, Wang B, Zuo Y-G, Qu T. Inhibitory effects of mizolastine on ultraviolet B-induced leukotriene B4 production and 5-lipoxygenase expression in normal human dermal fibroblasts in vitro. Photochem Photobiol 2006;82:665–669. [PubMed: 16402861]
42. Berdyshev EV, Schmid PC, Dong Z, Schmid HH. Stress-induced generation of N-acylethanolamines in mouse epidermal JB6 P+ cells. Biochem J 2000;346:369–374. [PubMed: 10677355]
43. Bak H, Hong SP, Jeong SK, et al. Altered epidermal lipid layers induced by long-term exposure to suberythemal-dose ultraviolet. Int J Dermatol 2011;50:832–837. [PubMed: 21699519]
44. Satoh T, Moroi R, Aritake K, et al. Prostaglandin D2 plays an essential role in chronic allergic inflammation of the skin via CRTH2 receptor. J Immunol 2006;177:2621–2629. [PubMed: 16888024]
45. Eberlein B, Eicke C, Reinhardt HW, Ring J. Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study). J Eur Acad Dermatol Venereol 2008;22:73–82. [PubMed: 18181976]
46. Broshtilova V, Gantcheva M. Therapeutic hotline: cysteinyl leukotriene receptor antagonist montelukast in the treatment of atopic dermatitis. Dermatol Ther 2010;23:90–93. [PubMed: 20136913]
47. Reines I, Kietzmann M, Mischke R, et al. Topical application of sphingosine-1-phosphate and FTY720 attenuate allergic contact dermatitis reaction through inhibition of dendritic cell migration. J Invest Dermatol 2009;129:1954–1962. [PubMed: 19194476]
48. Yuan C, Wang XM, Guichard A, et al. N-palmitoylethanolamine and N-acetylethanolamine are effective in asteatotic eczema: results of a randomized, double-blind, controlled study in 60 patients. Clin Interv Aging 2014;9:1163–1169. [PubMed: 25071367]
49. Maccarrone M, Di Rienzo M, Battista N, et al. The endocannabinoid system in human keratinocytes: evidence that anandamide inhibits epidermal differentiation through cb1 receptor-dependent inhibition of protein kinase c, activating protein-1, and transglutaminase. J Biol Chem 2003;278:33896–33903. [PubMed: 12815050]
50. Schaper K, Dickhaut J, Japtok L, et al. Sphingosine-1-phosphate exhibits anti-proliferative and anti-inflammatory effects in mouse models of psoriasis. J Dermatol Sci 2013;71:29–36. [PubMed: 23643308]
51. Kragballe K, Desjarlais L, Duell EA, Voorhees JJ. In vitro synthesis of 12-hydroxy-eicosatetraenoic acid is increased in uninvolved psoriatic epidermis. J Invest Dermatol 1986;87:47–52. [PubMed: 3088130]
52. Gudjonsson JE, Ding J, Li X, et al. Global gene expression analysis reveals evidence for decreased lipid biosynthesis and increased innate immunity in uninvolved psoriatic skin. J Invest Dermatol 2009;129:2795–2804. [PubMed: 19571819]
53. Kobayashi H, Katakura O, Morimoto N, Akiyoshi K, Kasugai S. Effects of cholesterol-bearing pullulan (CHP)-nanogels in combination with prostaglandin E1 on wound healing. J Biomed Mater Res Appl Biomater 2009;91:55–60.

54. Zheng D, Bode AM, Zhao Q, et al. The cannabinoid receptors are required for ultraviolet-induced inflammation and skin cancer development. Cancer Res 2008;68:3992–3998. [PubMed: 18483286]
55. Iwata C, Akimoto N, Sato T, Morokuma Y, Ito A. Augmentation of lipogenesis by 15-deoxy-δ12,14-prostaglandin J2 in hamster sebaceous glands: identification of cytochrome P-450-mediated 15-deoxy-δ12,14-prostaglandin J2 production. J Invest Dermatol 2005;125:865–872. [PubMed: 16297182]
56. Dobrosi N, Toth BI, Nagy G, et al. Endocannabinoids enhance lipid synthesis and apoptosis of human sebocytes via cannabinoid receptor-2-mediated signaling. FASEB J 2008;22:3685–3695. [PubMed: 18596221]
57. Alestas T, Ganceviciene R, Fimmel S, Muller-Decker K, Zouboulis CC. Enzymes involved in the biosynthesis of leukotriene B4 and prostaglandin E2 are active in sebaceous glands. J Mol Med (Berl) 2006;84:75–87. [PubMed: 16388388]
58. Cone EJ, Hillsgrove MJ, Jenkins AJ, Keenan RM, Darwin WD. Sweat testing for heroin, cocaine, and metabolites. J Anal Toxicol 1994;18:298–305. [PubMed: 7823536]
59. Czifra G, Szöllősi AG, Tóth BI, et al. Endocannabinoids regulate growth and survival of human eccrine sweat gland-derived epithelial cells. J Invest Dermatol 2012;132:1967–1976. [PubMed: 22513781]
60. Hussain JN, Mantri N, Cohen MM. Working up a good sweat – the challenges of standardising sweat collection for metabolomics analysis. Clin Biochem Rev 2017;38:13–34. [PubMed: 28798503]
61. Csosz E, Emri G, Kallo G, Tsaprailis G, Tozser J. Highly abundant defense proteins in human sweat as revealed by targeted proteomics and label-free quantification mass spectrometry. J Eur Acad Dermatol Venereol 2015;29:2024–2031. [PubMed: 26307449]
62. Rieg S, Steffen H, Seeber S, et al. Deficiency of dermcidin-derived antimicrobial peptides in sweat of patients with atopic dermatitis correlates with an impaired innate defense of human skin in vivo. J Immunol 2005;174:8003–8010. [PubMed: 15944307]
63. Jeje A, Koon D. An analysis on the rates and regulation of insensible water loss through the eccrine sweat glands. J Theor Biol 1989;141:303–324. [PubMed: 2630794]
64. Didierjean L, Gruaz D, Frobert Y, Grassi J, Dayer JM, Saurat JH. Biologically active interleukin 1 in human eccrine sweat: Site-dependent variations in α/β ratios and stress-induced increased excretion. Cytokine 1990;2:438–446. [PubMed: 2104237]
65. Fukumoto T, Tanaka T, Fujioka H, Yoshihara S, Ochi T, Kuroiwa A. Differences in composition of sweat induced by thermal exposure and by running exercise. Clin Cardiol 1988;11:707–709. [PubMed: 3224454]
66. Rittie L, Farr EA, Orringer JS, Voorhees JJ, Fisher GJ. Reduced cell cohesiveness of outgrowths from eccrine sweat glands delays wound closure in elderly skin. Aging Cell 2016;15:842–852. [PubMed: 27184009]
67. Jadoon S, Karim S, Akram MR, et al. Recent developments in sweat analysis and its applications. Int J Anal Chem 2015;2015:7.
68. Tremblay A, Simoneau JA, Bouchard C. Impact of exercise intensity on body fatness and skeletal muscle metabolism. Metabolism 1994;43:814–818. [PubMed: 8028502]
69. Swain DP, Leutholtz BC. Heart rate reserve is equivalent to %VO2 reserve, not to %VO2max. Med Sci Sports Exerc 1997;29:410–414. [PubMed: 9139182]
70. King CN, Senn MD. Exercise testing and prescription. Sports Med 1996;21:326–336. [PubMed: 8724201]
71. Strauss JS, Dowling DT, Ebling JF, Stewart ME. Sebaceous glands In: La G, ed. Physiology, Biochemistry and Molecular Biology of the Skin. New York: Oxford University Press;1991:712–740.
72. Taylor NAS, Machado-Moreira CA. Regional variations in transepidermal water loss, eccrine sweat gland density, sweat secretion rates and electrolyte composition in resting and exercising humans. Extrem Physiol Medv2013;2:4.

73. Baker LB, Stofan JR, Hamilton AA, Horswill CA. Comparison of regional patch collection vs. whole body washdown for measuring sweat sodium and potassium loss during exercise. J Appl Physiol 2009;107:887–895. [PubMed: 19541738]
74. Wu Y, Li L. Sample normalization methods in quantitative metabolomics. J Chromatogr A 2016;1430:80–95. [PubMed: 26763302]
75. Ryan D, Robards K, Prenzler PD, Kendall M. Recent and potential developments in the analysis of urine: A review. Anal Chim Acta 2011;684:17–29.
76. Tang KWA, Toh QC, Teo BW. Normalisation of urinary biomarkers to creatinine for clinical practice and research – when and why. Singapore Med J 2015;56:7–10. [PubMed: 25640093]
77. Montain SJ, Latzka WA, Sawka MN. Control of thermoregulatory sweating is altered by hydration level and exercise intensity. J Appl Physiol 1995;79:1434. [PubMed: 8593998]
78. Appenzeller BM, Schummer C, Rodrigues SB, Wennig R. Determination of the volume of sweat accumulated in a sweat-patch using sodium and potassium as internal reference. J Chromatogr B Analyt Technol Biomed Life Sci 2007;852:333–337.
79. Mishra A, Greaves R, Massie J. The relevance of sweat testing for the diagnosis of cystic fibrosis in the genomic era. Clin Biochemist Rev 2005;26:135–153.
80. Sigal CB, Dobson RL. The effect of salt intake on sweat gland function. J Invest Dermatol 1968;50:451–455. [PubMed: 5652824]
81. Schneider S, Ait MBZ, Schummer C, et al. Determination of fentanyl in sweat and hair of a patient using transdermal patches. J Anal Toxicol 2008;32:260–264. [PubMed: 18397579]
82. Schummer C, Appenzeller BM, Wennig R. Quantitative determination of ethyl glucuronide in sweat. Ther Drug Monit 2008;30:536–539. [PubMed: 18641544]
83. Hooton K, Li L. Non-occlusive sweat collection combined with chemical isotope labeling LC-MS for human sweat metabolomics and mapping the sweat metabolomes at different skin locations. Anal Chem 2017;89:7847–7851. [PubMed: 28679039]
84. Harris R, Jones HE, Artis WM. Orally administered ketoconazole: route of delivery to the human stratum corneum. Antimicrob Agents Chemother 1983;24:876–882. [PubMed: 6318663]
85. Peck CC, Conner DP, Bolden BJ, et al. Outward transcutaneous chemical migration: implications for diagnostics and dosimetry. Skin Pharmacol Physiol 1988;1:14–23.
86. Agrawal K, Bosviel R, Piccolo BD, Newman JW. Oral ibuprofen differentially affects plasma and sweat lipid mediator profiles in healthy adult males. Prostaglandins Other Lipid Mediat. Published Online: May 17, 2018 (doi: 10.1016/j.prostaglandins.2018.05.009)

Table 1.

Partial list of lipid mediators directly quantified in subjects with and without cutaneous disease. Unless otherwise specified, all lipid mediators were quantified in affected human skin. With the exception of the sphingolipids, concentrations of all lipid mediators increased in individuals with the disease compared to control.

Disease	Associated Cutaneous Lipid Mediators
Atopic Dermatitis	PGE2 (26), 12-HETE (26), 15-HETE (26), LTB4 (26, 27), LTC4 (27), LTE4 (27), PEA (28) †, OEA (28) †, AEA (28) †, 2-AG (28) †, total Ceramides (29), Sphingosine-1-Phosphate (30) †, 18:0 Sphingosine (31)
Contact Dermatitis	2-AG (32) ‡, 2-LG (32) ‡, 2-PG (32) ‡, 2-VG (32) ‡, PEA (33) ‡, AEA (34) ‡
Irritant Dermatitis	TXB2 (35), 12-HETE (35), SEA (35), OEA (35), LEA (35), PEA (35)
Psoriasis	PGE2 (36), PGF2a (36), 12-HETE (36), total Ceramides (37)
Wound Healing	PGE2 (38), PGD2 (38), AEA (39)
Sunburn	PGE1 (40), PGE2 (40), PGE3 (40), PGF2a (40), 8-HETE (40), 11-HETE (40), 12-HETE (40), 15-HETE (40), 13-HODE (40), LTB4 (41) §, AEA (42) ‡, LEA (42) ‡, PEA (42) ‡, SEA (42) ‡, OEA (42) ‡, VEA (42) ‡, total Ceramides (43) ‡

† Data generated from canine models

‡ Data generated from murine models

§ Data generated from cultured human fibroblast models

Table 2.

Partial list of lipid mediators and associated enzymes or receptors indirectly associated with cutaneous diseases.

Analytical Target	Association with Disease
Atopic Dermatitis	
PGD2 (44)	Modulates allergic inflammation via the CRTH2 pathway in a mouse model
PEA (45)	Cream containing 0.3% PEA caused significant improvement of symptoms in individuals with atopic dermatitis
Leukotriene receptor (46)	Montelukast (leukotriene receptor antagonist) successfully used as a treatment in individuals with atopic dermatitis
Contact Dermatitis	
Sphingosine-1-Phosphate (47)	Inhibits Langerhans cell migration response in a mouse model of allergic contact dermatitis
Asteatotic Eczema	
PEA and AEA (48)	Emollient cream containing 0.3% PEA and 0.2% AEA improved skin dryness, scaling and itching in individuals with atopic dermatitis compared to control emollient cream
Psoriasis	
AEA (49)	Inhibits keratinocyte differentiation and induces apoptosis in a human keratinocyte cell culture model
Sphingosine-1-Phosphate (50)	Topical application demonstrates anti-proliferative and anti-inflammatory effects in mouse models of psoriasis
12-LOX (51)	Increased activity determined in the skin of subjects with psoriasis, as *in vitro* synthesis of 12-HETE in uninvolved psoriatic skin biopsies was increased compared to control
15-LOX (52)	ALOX15B gene expression downregulated in lesional and non-lesional psoriatic skin biopsies
Wound Healing	
PGE1 (53)	PGE1 ointment in combination with cholesterol-bearing pullulan nanogels increased wound size reduction rates compared to control in a rat model
COX-1 (38)	Increased levels of COX-1 mRNA correlated with PGE2 and PGD2 synthesis during wound repair in a mouse model
CB1 and CB2 receptors (39)	Expression of CB1/CB2 receptors on fibroblasts and macrophage-like cells in granulation tissue is upregulated during wound healing in a rat model
Sunburn	
COX-1, COX-2, 12-LOX and 15-LOX (40)	Increased expression in the epidermis and/or dermis of ultraviolet-irradiated human skin compared to non-irradiated skin
5-LOX (41)	Ultraviolet-B irradiation of normal human dermal fibroblasts upregulates 5-LOX mRNA expression and translocation of 5-LOX from the nucleus to the cytoplasm
CB1 and CB2 receptors (54)	Ultraviolet irradiation causes activation of the CB1 and CB2 receptors in a mouse model
Acne Vulgaris	
15d-PGJ2 (55)	Stimulates sebocyte lipogenesis by augmenting triglyceride synthesis in a sebocyte cell culture model
AEA and 2-AG (56)	Enhances lipid synthesis in a sebocyte cell culture model in a manner resembling acne vulgaris
LTA_4 hydrolase and 5-LOX (57)	Increased expression in advanced differentiated sebocytes and cells of the ductus seboglandularis in lesional skin collected from individuals with acne compared to control
COX-2 (57)	Increased expression in undifferentiated and early differentiated sebocytes, and cells of the ductus seboglandularis in lesional skin collected from individuals with acne compared to control