Gene expression of sphingolipid metabolism pathways is altered in hidradenitis suppurativa

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Background: Hidradenitis suppurativa (HS) is a debilitating skin disease characterized by painful recurrent nodules and abscesses caused by chronic inflammation. Early events in the development of HS are believed to occur in the folliculopilosebaceous unit; however, the signaling pathways behind this mechanism are unknown. Sphingolipids, such as ceramide, are essential components of the skin and appendages and have important structural and signaling roles.

Objective: We sought to explore whether the gene expression of enzymes involved in sphingolipid metabolic pathways is altered in HS.

Methods: A microarray data set including 30 samples was used to compare the expression of sphingolipid-related enzymes in inflammatory skin lesions from HS patients (n = 17) with the expression in clinically healthy skin tissue (n = 13). Differential expression of sphingolipid metabolism–related genes was analyzed using Gene Expression Omnibus 2R.

Results: HS lesional skin samples have significantly decreased expression of enzymes generating ceramide and sphingomyelin, increased expression of enzymes catabolizing ceramide to sphingosine, and increased expression of enzymes converting ceramide to galactosylceramide and gangliosides.

Limitations: Limitations of this study include assessing the expression of sphingolipid-related enzymes without assessing the levels of the related sphingolipids.

Conclusion: Our study suggests that sphingolipid metabolism is altered in HS lesional skin compared with normal skin. (J Am Acad Dermatol 2017;77:268-73.)

Key words: ceramide; hexosylceramide; hidradenitis suppurativa; lipid metabolism; perilipin; sphingolipids.

Hidradenitis suppurativa (HS) is a debilitating skin disease characterized by painful and recurrent nodules and abscesses caused by chronic inflammation.[1,2] The abscesses can rupture resulting in the formation of painful sinus tracts and scarring,[3,4] which can become a burden psychologically and negatively impact the patient's quality of life.[5,6] Recent evidence shows that HS is a chronic systemic disease and is not limited to skin problems.[7,8] For instance, patients with HS also have cardiovascular risk factors such as metabolic syndrome, obesity, smoking, and dyslipidemia.[7-11] Even though HS affects around 1% of the population,

Abbreviations used:

CerS1-6:	ceramide synthase 1-6
GEO2R:	Gene Expression Omnibus 2R
HS:	hidradenitis suppurativa
NK:	natural killer
PKA:	protein kinase A
S1P:	sphingosine-1-phosphate
SK:	sphingosine kinase

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the pathophysiology of the disease is not yet well understood.

Histologically, HS is characterized by follicular hyperplasia, ductal hyperkeratosis, perifollicular inflammation, and sinus tract formation.[12,13] HS is believed to be initiated by an event occurring in the folliculopilosebaceous unit.[4,13,14] However, the exact location of the primary inflammatory process is still under debate. Some studies have demonstrated that inflammation in HS starts in the follicular portion after follicular hyperplasia and occlusion.[14-16] On the other hand, one recent study showed that the primary event is an alteration in the basement membrane zone surrounding the folliculopilosebaceous unit.[17]

CAPSULE SUMMARY

- The signaling pathways underlying hidradenitis suppurativa (HS) pathogenesis are poorly understood.
- HS lesional skin has decreased levels of ceramide generating enzymes and increased levels of enzymes generating galactosylceramide and gangliosides.
- Sphingolipid metabolism might represent a possible target for drug discovery in HS.

Sphingolipids are a family of membrane lipids that play roles regulating the fluidity and subdomain structure of the lipid bilayer.[18] Recent evidence shows that several sphingolipid species such as ceramide and sphingosine-1-phosphate (S1P) act as biologically active signaling molecules.[19]

The bioactive sphingolipid ceramide is composed of a sphingosine backbone that is esterified to a fatty acyl chain through an amide linkage at carbon 3.[20,21] The variety in the length of the fatty acyl chain generates many different ceramides, C_{14}- through C_{26}-ceramides.[21] Ceramide lies at the center of sphingolipid metabolism, acting as a substrate for the generation of more complex sphingolipids (Fig 1). Ceramide can be converted to sphingomyelin by sphingomyelinase enzymes, to ceramide-1-phosphate by ceramide kinase, to hexosylceramides by hexosylceramidase enzymes,[22] and to complex glycosphingolipids and gangliosides by ganglioside GM synthase enzymes.[23]

De novo generation of ceramide requires the enzymatic action of ceramide synthases 1-6 (CerS1-6).[24,25] Ceramide catabolism is regulated mainly by ceramidases, which cleave ceramide to generate sphingosine. Sphingosine then becomes phosphorylated by sphingosine kinases 1 or 2 (SK1 or SK2) to produce the other biologically active sphingolipid, S1P.[26] S1P can be secreted into the extracellular matrix and act as an autocrine or paracrine biologic substance by binding to S1P receptors 1-5. The major downstream responses are related to increased inflammation, cell migration, and angiogenesis.[27]

Ceramide metabolism plays an important role in skin biology.[28-30] CerS3 has been shown to fulfill an essential function during skin development.[30] In addition, loss of CerS4 in CerS4-deficient mice (Cers4-/-) alters the lipid composition of sebum.[31] The modified sebum blocks the hair canal resulting in progressive hair loss.[31] Indeed, mice at 12 months old display additional epidermal tissue destruction due to dilated and obstructed pilary canals.[31-34] Interestingly, topical ceramide creams have been used to repair the skin barrier and have demonstrated success in the treatment of skin diseases such as atopic dermatitis and acne.[35,36]

We hypothesized that the homeostasis of sphingolipid metabolism might be altered in HS. We tested this hypothesis by assessing the gene expression of the enzymes participating in the sphingolipid metabolism pathways in normal skin versus skin lesions obtained from HS patients using an mRNA microarray dataset.

METHODS

We downloaded the gene expression profile GSE72702 from Gene Expression Omnibus database,[37] in which a total of 30 chips were available: inflammatory skin lesions from HS patients (n = 17) and clinically healthy skin tissue from HS patients (n = 13).[38] Differential expression of sphingolipid metabolism–related genes was identified using Gene Expression Omnibus 2R (GEO2R), which performs analyses using GEOquery and limma R packages from the Bioconductor project. Gene expression of lesional and healthy skin was compared.

The distribution of the gene expression values was calculated using GEO2R. Samples were suitable for comparison, with median-centered values indicative that the data were normalized and cross-comparable. GEO2R generates the following values:

- An adjusted *P* value based on the Benjamini and Hochberg false discovery rate. To correct for the occurrence of false positive results, a *P* value $<.05$ is considered statistically significant.
- A B-statistic, which is the log odds that the gene is differentially expressed between nonlesional and lesional skin.