

Despite the fact that acne may be the most common skin disease, it is clear that there are missing pieces in its puzzling pathogenesis. This excellent work by Kistowska *et al.* (2014) validates the recent work of Qin *et al.* (2014) and takes the field one step closer to understanding the immunologic mechanisms at play in acne. Important next steps would be to examine the mechanisms by which *P. acnes* activates the innate immune response within the unique microenvironments that arise during acne lesion development and to examine the respective roles of IL-1 α and IL-1 β in this process.

CONFLICT OF INTEREST

The author states no conflict of interest.

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The Adverse Effect of IFN Gamma on Stratum Corneum Structure and Function in Psoriasis and Atopic Dermatitis

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There is a marked increase in cytokines, including interferon gamma, in cutaneous diseases such as atopic dermatitis and psoriasis. In this issue of the Journal, Tawada and colleagues demonstrate that the quantity of ultra long-chain ceramides in the stratum corneum, which play a key role in maintaining the permeability barrier, is reduced in atopic dermatitis and psoriasis. Further, they demonstrate that interferon gamma decreases the expression of the enzymes required for the synthesis of these ultra long-chain ceramides (ELOVLs and ceramide synthase 3). These results suggest that an increase in interferon gamma by decreasing the key enzymes required for the synthesis of ultra long-chain ceramides could further impair permeability barrier function, thereby exacerbating the pathological changes.

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It has long been recognized that cytokines, such as tumor necrosis factor (TNF), IL-1, IL-6, and the IFNs, regulate lipid metabolism (Hardardottir *et al.*, 1994; Khovidhunkit *et al.*, 2004). Studies in the 1980s demonstrated that TNF and other cytokines would inhibit fat accumulation in adipocytes by decreasing the activity of lipoprotein lipase and by inhibiting fatty acid synthesis. In contrast, in the liver, TNF

and other cytokines stimulate lipid synthesis and VLDL production, which contributes to the elevation in serum triglyceride levels that characteristically occurs during infections and inflammatory diseases. Over the ensuing years, cytokines have been shown to affect a large number of different lipid metabolic pathways in a wide variety of tissues (Hardardottir *et al.*, 1994; Khovidhunkit *et al.*, 2004). Not surpris-

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Clinical Implications

- Molecular understanding of IFN gamma effects on the stratum corneum now presents possibilities for treating patients with both psoriasis and atopic dermatitis.
- Inhibiting the action of IFN gamma, providing ultra long-chain ceramides, or using drugs to stimulate the expression of ELOVS and CerS3 could well be beneficial for such patients.
- No one would have predicted 30 years ago that new molecular knowledge about a surface membrane 10- μ m thick might lead to such useful insight.

singly, cytokines can also regulate various aspects of lipid metabolism in the epidermis.

Following permeability barrier disruption, there is a marked increase in the expression of TNF, IL-1, IL-6, IL-8, IL-10, and IFN gamma in the epidermis, with no change in IL-2, IL-3, IL-4, or IL-5 expression (Wood *et al.*, 1992; Nickoloff and Naidu, 1994; Wood *et al.*, 1997). Furthermore, increases in these cytokines accelerate permeability barrier repair by stimulating the synthesis of lipids that are required for the formation of lamellar bodies and restoration of lamellar membranes in the stratum corneum (Feingold and Denda, 2012). Thus, increased cytokine production following permeability barrier perturbation can have beneficial effects, and the failure to increase cytokine production can have adverse effects. For example, restoration of permeability barrier function is delayed in aged mice owing to a decrease in the expression of IL-1 alpha, leading to reduced lipid synthesis in keratinocytes (Ye *et al.*, 2002; Barland *et al.*, 2004). Treatment with IL-1 accelerates permeability barrier recovery following its disruption (Barland *et al.*, 2004).

There is a marked increase in the expression of a wide variety of cytokines in cutaneous diseases such as psoriasis and atopic dermatitis. Although following acute permeability barrier disruption the increase in cytokines is beneficial in these chronic disorders, it is likely that the increase in cytokine production could affect lipid metabolism adversely and thereby contribute to skin pathology. For example, Hatano *et al.* (2005) and Sawada *et al.* (2012) have both shown that IL-4 inhibits the expression of acid sphingomyelinase and

beta-glucocerebrosidase, resulting in a decrease in ceramide levels in the stratum corneum (Hatano *et al.*, 2005, 2007; Sawada *et al.*, 2012). This results in increased transepidermal water loss, a marker of impaired permeability barrier function.

In this issue of the Journal, Tawada *et al.* (2014) provide evidence that IFN gamma has an important role in inducing alterations in ceramide composition in the stratum corneum of patients with atopic dermatitis and psoriasis. Using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, the authors demonstrate that the quantity of high total carbon number ceramides is reduced in both psoriasis and atopic dermatitis, compared with normal controls (i.e., shorter fatty acid chain length in patients with these cutaneous diseases). The results described by Tawada *et al.* (2014), in patients with atopic dermatitis, confirms earlier reports that have also noted a decrease in fatty acid chain length in ceramides (Elias, 2013; van Smeden *et al.*, 2013). In addition, recent studies have shown further a decrease in long-chain free fatty acids in the stratum corneum from patients with atopic dermatitis (Park *et al.*, 2012). Although previous studies in patients with psoriasis have reported decreases and increases in specific subclasses of ceramides, this is the first report of a decrease in fatty acid chain length (van Smeden *et al.*, 2013). Thus, two very common cutaneous disorders demonstrate an inability to synthesize ceramides that contain long-chain fatty acids, which contributes to the well-recognized impairment in permeability barrier function that is seen in patients with both disorders.

Fatty acid synthesis normally results in fatty acids that are 16 carbon atoms in length. To create longer fatty acids, fatty acid elongation is required, which is mediated by four reactions that occur in the endoplasmic reticulum. The first step is rate limiting and is catalyzed by a family of seven enzymes (elongation of very long-chain fatty acids, ELOVLs; Rabionet *et al.*, 2013). The different ELOVLs have preference based on fatty acid chain length (Rabionet *et al.*, 2013). For example, ELOVL 1 prefers fatty acids C18–24, whereas ELOVL 4 favors fatty acids with a chain length >24 carbons. The synthesis of fatty acids longer than 24 carbons requires ELOVL4. In mice, ELOVL 1, 3, 4, and 7 are expressed in the skin (Rabionet *et al.*, 2013). Both ELOVL 1 and ELOVL 4 knockout mice have impaired permeability barrier function, and they die shortly after birth owing to decreased ultra long-chain ceramides, resulting in abnormal lamellar membranes in the stratum corneum (Rabionet *et al.*, 2013). Thus, the synthesis of ceramides that contain long-chain fatty acids in the epidermis requires ELOVLs.

In addition to ELOVLs, the synthesis of ceramides that contain long-chain fatty acids also requires ceramide synthase 3 (CerS3; Rabionet *et al.*, 2013). The pathway for the biosynthesis of ceramides is shown in Figure 1, and CerS catalyzes the attachment of acyl-CoAs with dihydrosphingosine. The CerS family consists of six genes, and these enzymes have preferences for acyl-CoA substrates (Rabionet *et al.*, 2013). CerS3 has a unique preference for C26 and C28 acyl-CoAs. CerS3 knockout mice die shortly after birth from an impaired permeability barrier, and, similar to ELOVL 1 and 4 knockout mice, have decreased ultra long-chain ceramides and abnormal lamellar membranes (Rabionet *et al.*, 2013). Thus, both ELOVLs and CerS3 are required for the synthesis of ceramides that contain long-chain fatty acids, and ultra long-chain ceramides are essential for normal permeability barrier function.

The paper by Tawada *et al.* (2014) in the current issue tested the effect of a number of different cytokines on the expression of ELOVLs and CerSs. They report that IFN gamma reduced the

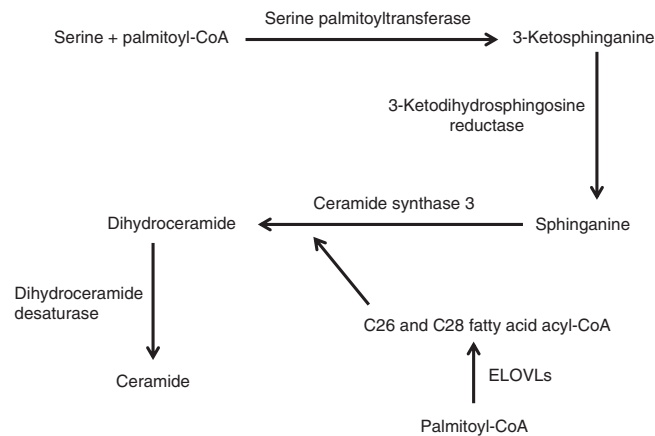


Figure 1. The biosynthesis of ultra long-chain ceramides.

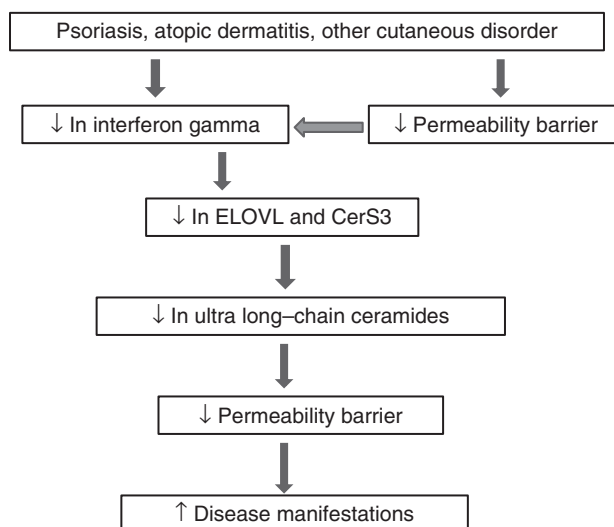


Figure 2. Pathway by which IFN gamma leads to an abnormal permeability barrier.

expression of ELOVL 4 and 5 and CerS3 and 6 in cultured human keratinocytes. Notably, other cytokines, including TNF, IL-1, IL-4, and IL-6, did not affect the expression of these enzymes. In addition, in human epidermal equivalent cultures, IFN gamma treatment reduced the expression of ELOVL 1, 4, 6, and 7 and CerS3, 4, and 6. Significantly, the quantity of ceramides containing long-chain fatty acids was decreased in the stratum corneum of three-dimensional epidermal sheets treated with IFN gamma. These results suggest that an increase in IFN gamma, which is well known to occur in patients with psoriasis, atopic dermatitis, and other cutaneous diseases, could lead to alterations in the expression of key

enzymes, ELOVLs and CerS3, which thereby result in abnormalities in the synthesis of ceramides containing long-chain fatty acids, leading to impaired permeability barrier function that could further exacerbate the pathologic changes (Figure 2). It is noteworthy that a decrease in ELOVLs has been reported in patients with psoriasis and in an animal model of atopic dermatitis (Gudjonsson *et al.*, 2010; Park *et al.*, 2012). It is likely that changes in the expression of other cytokines could also result in alterations in lipid metabolism that adversely affect permeability barrier function. For example, as noted above, an increase in IL-4 in atopic dermatitis decreases ceramide production by inhibiting the expression of acid sphingo-

myelinase and beta-glucocerebrosidase (Hatano *et al.*, 2005; Hatano *et al.*, 2007; Sawada *et al.*, 2012).

It should be recognized that the changes reported in the paper by Tawada *et al.* (2014) are not the primary abnormalities that lead to the pathologic changes and clinical manifestations in patients with psoriasis or atopic dermatitis. In the case of atopic dermatitis, the primary abnormality in many patients results from abnormalities in the filaggrin gene and, in a small number of patients, in genes regulating serine protease activity or anti-protease activity (Elias, 2013). In the case of psoriasis, the primary abnormality is still uncertain. Regardless, the primary abnormality leads to inflammation and abnormal permeability barrier function, both of which increase epidermal cytokine production. The increase in cytokines can have beneficial effects and adverse consequences. Tawada *et al.* (2014) demonstrate that an increase in IFN gamma can decrease the expression of key enzymes required for the synthesis of ultra long-chain ceramides, which are required for the formation of a normal permeability barrier. The decrease in ultra long-chain ceramides can result in abnormal permeability barrier function or worsen a deficient permeability barrier. Abnormal permeability barrier function can further increase the epidermal production of cytokines including IFN gamma, leading to a positive-feedback system that can exacerbate disease manifestations (Figure 2). Perhaps inhibiting the action of IFN gamma, providing ultra long-chain ceramides, or using drugs to stimulate the expression of ELOVLs and CerS3 could have a beneficial effect in patients with psoriasis, atopic dermatitis, or other cutaneous diseases where IFN production is increased.

CONFLICT OF INTEREST

The author states no conflict of interest.

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PHIPing Out: A Genetic Basis for Tumor Ulceration

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Ulceration is a common negative prognostic marker of solid tumors including melanoma. The signaling basis of ulceration is being elucidated. PHIP has been found to be amplified in wild-type melanomas, resulting in Akt activation and aerobic glycolysis (Warburg effect), associated with ulceration. The ulceration phenotype likely represents the genotype of the reactive oxygen driven tumor, in which reactive oxygen drives angiopoietin-2 production, tumor growth, and invasion. This phenotype is amenable to pharmacologic intervention.

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Ulceration is a common phenomenon in dermatology and an adverse prognostic factor in melanoma. For many years,

ulceration has been described as “a tumor outgrowing its blood supply”. However, if blood supply is insufficient,

why is ulceration an adverse prognostic factor? We have shown that the majority of cutaneous ulcers are not due to insufficient vascularity, but due to excess vascularity (Arbiser *et al.*, 2003). High levels of matrix metalloproteinases and unstable vasculature result in a “hostile” environment for epithelialization, leading to ulceration (Munavalli *et al.*, 2003). Ultimately, the factors that promote ulceration are not well understood.

Kashani-Sabet *et al.* have now identified pleckstrin homology domain-interacting protein (PHIP) copy number, initially as the top-rated gene differentially expressed between metastatic melanoma and primary melanoma (Bezrookove *et al.* 2014). In this study, they characterized PHIP as being expressed at high levels in ulcerated melanomas. Not only was it present, the investigators also demonstrated functional consequences of PHIP overexpression. Inhibition of PHIP led to a decrease in aerobic glycolysis (Warburg effect). The Warburg effect is commonly associated with defective glucose metabolism, with glucose being metabolized to lactate instead of full metabolism through to respiration. Although the ineffective metabolism of glucose is initially counter-intuitive in terms of tumor growth, more recent studies have established that tumor cells gain certain survival advantages in exchange for switching to aerobic glycolysis, namely NF- κ B activation and the ability to survive under extreme hypoxia (Govindarajan *et al.*, 2007). The authors demonstrated the downregulation of biomarkers of the Warburg phenomenon, including LDH5, HIF1 α , and VEGF.

Although this study demonstrates PHIP elegantly as a potential therapeutic target, several questions can be asked that might provide elaboration and answers about the role of PHIP in melanoma. First, is amplification the sole mechanism of increased PHIP expression? If this is the case, adjacent genes might provide advantages to melanoma, because coamplification might increase the expression of PHIP and an additional gene in a single step. Second, what are the signaling pathways downstream of PHIP amplification? Glycolysis is associated in melanoma with the reactive oxygen-driven phenotype, in

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