Saturated Fatty Acids as Possible Key Amplifiers of Psoriatic Dermatitis

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The association of obesity with psoriasis is well known, but the molecular link between these two entities is incompletely characterized. Herbert et al. report that dietary saturated fatty acids, rather than obesity itself, promote exacerbation of psoriasis in high fat diet-induced obesity. They also suggest that dietary manipulation could improve psoriasis.

Journal of Investigative Dermatology (2018) **138,** 1901–1903. doi:10.1016/j.jid.2018.07.004

Psoriasis represents an inflammatory disease, or a group of related inflammatory skin diseases, that affects up to 3% of the population. Although a great deal about the etiology of psoriasis remains unknown, multiple factors including family history, smoking, and obesity have been associated with its development (Naldi et al., 2005). Regarding the association of psoriasis and obesity, 16 observational studies with a total of 2.1 million participants were conducted between 1980 and 2012. In aggregate, results showed an association between body mass index and the severity or frequency of psoriasis (Armstrong et al., 2012). However, the precise molecular mechanisms that explain this association are not well understood.

Because obesity is associated with psoriasis and other systemic diseases, such as diabetes and atherosclerosis, an increase in systemic inflammation induced by adipokines has been proposed as a relevant mechanism. In obesity, visceral adipose tissues expand and produce various adipokines including IL-6, tumor necrosis factor (TNF)-α, and leptin. Because these cytokines, especially TNF-α, play central roles in the development of psoriatic dermatitis, it is suggested that a systemic increase of adipokines in obesity may worsen psoriasis (Sterry et al., 2007). However, recent studies using a murine psoriasis model have suggested that dietary components, rather than obesity, may exacerbate factors in psoriasis (Nakamizo et al., 2017; Stelzner et al., 2016; Vasseur et al., 2016; Zhang et al., 2015).

> Manipulation of dietary saturated fatty acids may represent a new therapeutic strategy for psoriasis treatment.

Saturated fatty acids (SFAs) or polyunsaturated fatty acids (PUFAs), which are abundant in a high fat diet (HFD), are suspected to be exacerbating factors, and an HFD is proposed to be a major contributor to obesity. It has been shown that psoriasis patients consume significantly more total fat and SFAs than healthy control individuals (Zamboni et al., 1989). In addition, clinical studies have shown that low calorie and low fat diets lead to improvement in psoriasis symptoms (Rucevic et al., 2003).

Results obtained with mouse psoriasis models suggest several alternative mechanisms to explain the HFD-induced exacerbation of psoriatic dermatitis. In HFD-fed mice, blood free fatty acids (FFAs) were significantly elevated, and their concentrations correlated with the severity of psoriatic dermatitis (Stelzner et al., 2016). SFAs in HFD are reported to exacerbate psoriatic dermatitis by promoting T helper (Th) 1/Th17 differentiation via activation of dendritic cells (Stelzner et al., 2016; Zhang et al., 2015). Consistently, IL-17–producing cells were increased in the skin and the regional lymph nodes in HFD-fed mice (Nakamizo et al., 2017; Vasseur et al., 2016; Zhang et al., 2015). SFAs also facilitate CCL20 production from keratinocytes and dermal blood vessels and promote the accumulation of IL-17–producing cells in the skin (Nakamizo et al., 2017). Thus, several studies suggest that SFAs in HFD may be causative factors that exacerbate psoriasis.

Using a mouse psoriasis model, Herbert et al. (2018) provide evidence that regulation of dietary SFAs attenuates psoriatic dermatitis. They first examined the relationship between various blood markers associated with obesity (including FFAs, hemoglobin A1c, and insulin) and the severity of psoriasis. They determined that only concentrations of FFAs correlated with the severity of psoriasis (Herbert et al., 2018). Next, they assessed effects of an HFD on psoriatic dermatitis in mice. Mice fed with an HFD for 20–25 weeks, which led to increased body weight, developed more severe skin inflammation than the control normal diet-fed mice. As previously observed in human psoriasis, the severity of skin inflammation and the concentration of FFAs in the blood of HFD-fed mice were positively correlated (Herbert et al., 2018). HFD-fed mice experienced exacerbated skin inflammation after only short-term (5 weeks) exposure to an HFD. At this timepoint, among the various obesity-related parameters (including body weight, body fat, blood glucose level, and FFA levels), only the concentrations of FFAs in blood were significantly increased in

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HFD-fed mice compared with normal diet-fed mice. Herbert et al. further characterized FFAs in the blood of HFD-fed mice and detected increases in SFAs such as palmitic acid and stearic acid. No increases in PUFAs, such as oleic acid and linoleic acid, were found. Analysis of cytokine profiles in skin showed increases in selected cytokines (IL-1, IL-6, and TNF-α) without elevation of central mediators of psoriatic dermatitis including IL-17 and IL-23. These results suggested that dietary SFAs, rather than obesity, were responsible for the worsening of psoriatic dermatitis and that this occurred independent of the IL-23/IL-17 axis.

To further examine the causal relationship between the SFAs and the HFD-induced exacerbation of psoriatic dermatitis, Herbert et al. (2018) tested a carefully designed intervention (Figure 1). First, mice were fed with a standard HFD (high-SFA) for 2.5 weeks. Then, either the HFD was continued or a modified HFD containing lower levels of SFAs was instituted for another 2.5 weeks. Compared with mice fed with a standard HFD, mice fed with the modified HFD showed significantly lower levels of SFA in the blood, and they did not experience HFD-induced exacerbations of psoriatic dermatitis.

The modified HFD in the described experiment was enriched with PUFAs, which are reported to have anti-inflammatory effects. To determine if the protection from exacerbation by the modified HFD was due to the effects of reduced dietary SFAs alone or the increased ingestion of PUFAs, Herbert et al. (2018) performed another diet change experiment in which mice were fed a standard HFD for 20–25 weeks and then a low fat chow diet (containing low SFA and low PUFA levels) for 1 week. This dietary change again decreased the concentration of SFAs in the blood and suppressed the HFD-induced exacerbation of psoriatic dermatitis. Taken together, the experiments by Herbert et al. constitute strong evidence that dietary SFA, rather than obesity itself, are key amplifiers of psoriatic dermatitis, and suggest that reduction of dietary SFAs may attenuate psoriatic dermatitis (Figure 2).

Although these findings by Herbert et al. (2018) are striking and provocative, there are several unresolved issues. First, the protocol for the induction of psoriatic dermatitis in mice is unconventional, because imiquimod (IMQ) was applied only once, and analysis of skin inflammation was performed 3 days later. Typically, IMQ is applied for 5–7 consecutive days to induce psoriatic dermatitis. In addition, because the development of human psoriasis and the IMQ-induced mouse psoriasis model depends on IL-17, it is not clear whether the elevation of IL-1β or IL-6 in the skin of HFD-fed mice is a reasonable surrogate for exacerbation of psoriatic dermatitis. Second, the mechanisms by which SFAs exacerbate psoriatic dermatitis remain obscure. Herbert et al. detected elevations of cytokines in the skin and myeloid skin

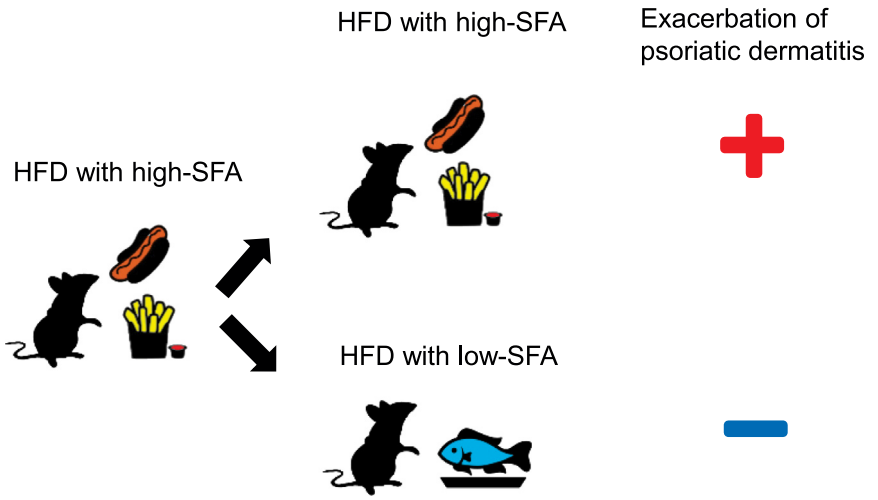

Figure 1. Reduction of dietary saturated fatty acids diminishes the exacerbation of psoriatic dermatitis under high fat diet feeding. Mice fed with standard high fat diet (HFD), which contains high amount of saturated fatty acids (SFAs), exhibit exacerbated psoriatic dermatitis. When the diet is changed to a modified HFD, which contains low amount of SFAs, the exacerbation of psoriatic dermatitis diminishes. HFD, high fat diet; SFA, saturated fatty acid.

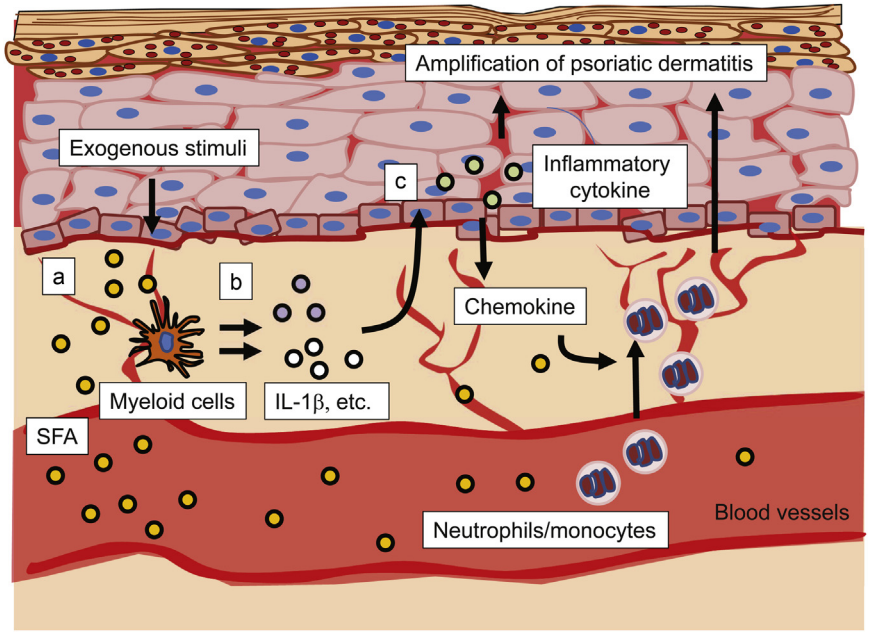

Figure 2. Possible mechanisms of SFA-induced exacerbation of psoriatic dermatitis. (**a**) SFAs in the blood are transported in the skin and act on myeloid cells in the skin. (**b**) SFAs, together with exogenous stimuli, then induce the production of various proinflammatory cytokines, such as IL-1β, from myeloid cells. (**c**) The proinflammatory cytokines facilitate the expression and secretion of chemokines and inflammatory cytokine from keratinocytes and induce the amplification of psoriatic dermatitis. SFA, saturated fatty acid.

cells of HFD-fed mice and propose that SFAs sensitize myeloid cells to produce proinflammatory cytokines, thereby exacerbating dermatitis. However, the cell populations that are affected by SFAs have not been identified. In addition, although Herbert et al. performed in vitro experiments that relate to the in vivo findings, the cells used in the culture systems were myeloid "peritoneal" cells. It is therefore uncertain if the in vitro findings can be directly translated to the skin myeloid cells. The concentrations and localization of SFAs in the skin after HFD feeding also need to be defined.

The reasons for the discrepancy between the results of Herbert et al. (2018) and those of previous studies are also unclear. For example, it has been reported that skin T cells and macrophages are increased by feeding mice an HFD (Nakamizo et al., 2017; Vasseur et al., 2016; Zhang et al., 2015), yet no changes in skin cell composition were observed in this study. This may relate to different HFDs that were used in different studies. The HFD used in the study by Herbert et al. was made from coconut oil, whereas other studies have used HFDs derived from lard (Nakamizo et al., 2017; Zhang et al., 2015) and cocoa butter (Vasseur et al., 2016). Differences in environmental factors, such as the microbiomes in the skin or in the gut, may also affect the phenotypes of HFD-fed mice. Additional investigation of these issues will provide new insights into the pathogenesis of psoriasis and the role of SFAs in it.

The proposal by Herbert et al. (2018) that dietary SFAs exacerbate psoriasis and that alternation of the diet may lead to the improvement of psoriasis is important. Although further experiments are required to confirm the applicability of their findings to human psoriasis and to elucidate the mechanisms of action of SFAs in skin, dietary changes may become an important therapeutic strategy for psoriasis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Psoriasis Plays a Wild CARD

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Rare autosomal mutations in *CARD14* have previously been linked to psoriasis susceptibility in humans, but their pathogenic role had not been shown. Mellett et al. generated mice harboring the patient-derived gain-of-function *Card14ΔE138* mutation and showed that hyperactivation of CARD14 alone is sufficient to induce immunopathogenic mechanisms that are responsible for psoriasis, which is driven by the IL-17/IL-23 axis.

Journal of Investigative Dermatology (2018) **138,** 1903–1905. doi:10.1016/j.jid.2018.05.001

Psoriasis is a common chronic inflammatory skin disease that has a serious impact on the quality of life of affected patients. Plaque psoriasis, which is the most common type of psoriasis and is also known as psoriasis vulgaris, is characterized by the emergence of red, scaly, and sharply demarcated plaques that result from the pathogenic interplay between hyperproliferative keratinocytes and activated immune cells. Less common types of psoriasis include pustular, inverse, erythrodermic, and guttate psoriasis. Genome-wide association studies have shown that genetic factors play an important role in the etiology of psoriasis. Rare highly penetrant mutations in *CARD14* have been associated with plaque psoriasis, and *CARD14* accounts for the elusive *PSORS2* locus association (Jordan et al., 2012b). *CARD14* mutations have also been linked to clinically related conditions such as psoriatic arthritis, generalized pustular psoriasis, and pityriasis rubra pilaris (reviewed by Van Nuffel et al., 2017). CARD14 is an intracellular

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