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Invited Review Article

Current understanding of the role of dietary lipids in the pathophysiology of psoriasis

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ABSTRACT

Dietary lipids are fundamental nutrients for human health. They are typically composed of various long-chain fatty acids which include saturated fatty acids (SFAs) and unsaturated fatty acids (UFAs). UFAs are further classified into several groups, such as omega-3 polyunsaturated fatty acids (PUFAs) and omega-6 PUFAs, depending on their chemical structure. Epidemiological studies have suggested the involvement of dietary lipids in the progression or regulation of psoriasis, a common chronic inflammatory skin disease induced via the IL-23/IL-17 axis. Although the underlying mechanisms by which dietary lipids regulate psoriasis have remained unclear, with the advancement of experimental techniques and the development of psoriasis mouse models, various possible mechanisms have been proposed. For example, SFAs may facilitate psoriatic dermatitis by causing activation of the inflammasome in keratinocytes and macrophages or by inducing IL-17-producing cells, such as Th17 and IL-17-producing γδ T cells in the skin, while omega-3 PUFAs may play inhibitory roles by suppressing Th17 differentiation. In this review, we summarize current data on the roles of dietary lipids in the development of psoriasis as revealed by mouse studies, and we discuss potential therapeutic strategies for psoriasis from the perspective of dietary lipids.

1. Introduction

Dietary lipids are essential nutrients for maintaining our health. They can be a source of energy, a component of cellular membranes, and they facilitate various intra and extra cellular signaling pathways as lipid mediators. Dietary lipids are typically composed of glycerol and long chain fatty acids. Fatty acids are classified into two groups: saturated fatty acids (SFAs) and unsaturated fatty acids (UFAs). The characteristic chemical structure of SFAs is that all of the carbons are attached to each other by single bonds, while at least one pair of carbons is connected by a double bond in UFAs. UFAs with only one double bond are called monounsaturated fatty acids, and UFAs with more than one double bond are called polyunsaturated fatty acids (PUFAs). PUFAs are further classified into several groups, such as omega-3 PUFAs and omega-6 PUFAs, depending upon the position of the first double bond with respect to the omega end (Fig. 1).

The composition of FAs in dietary lipids significantly differs among diets [1]. SFAs, such as palmitic acids and stearic acids, are abundant in meat, butter and palm oil. Fish and nuts are rich in omega-3 PUFAs (e.g., α-linolenic acids, eicosapentaenoic acids (EPAs) and docosahexaenoic acids (DHAs)). Omega-6 PUFAs, which include linoleic acids and arachidonic acids, are found in various diets but are particularly prevalent in dietary oils, such as safflower oil or soy oil. Because omega-3 PUFAs and omega-6 PUFAs are not synthesized by mammals, they must be obtained from the diet. These SFAs and PUFAs in diets play important roles not only for the maintenance of homeostasis but also for the regulation of various diseases in diverse organs, including the skin [2].

Psoriasis is one of the most common, chronic inflammatory skin diseases with a prevalence of 1–2% worldwide [3,4]. Patients with psoriasis exhibit clear demarcated erythema with thick scales on the entire body, which severely impairs our quality of life. Although the precise pathogenesis remains

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unknown, cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-23 and IL-17, play important roles in the development of psoriasis [5]. Biologics that target these cytokines are in clinical use and exert significant therapeutic effects in psoriasis [6]. TNF-α and IL-23 produced by inflammatory dendritic cells in the skin induce activation of Th17 cells to produce IL-17 in the skin. IL-17 then acts on keratinocytes and induces their activation to produce various cytokines and chemokines, which further recruit inflammatory cells to the skin. Although appropriate mouse models of psoriasis have been lacking, a mouse model using an imiquimod (IMQ)-containing cream was recently developed [7] and is now widely used as a convenient model of psoriasis. IMQ is an agonist for toll-like receptor 7. Daily application of IMQ-containing cream to the mouse skin causes dermatitis through the IL-23/IL-17 axis, similar to psoriasis. Using this model, the involvement of dietary lipids in the development of psoriatic dermatitis has been investigated, and various regulatory mechanisms have been proposed.

In this review, we describe the current investigative status on the role of dietary lipids in the pathophysiology of psoriasis and discuss the clinical potential of manipulating dietary lipids for the treatment of psoriasis.

2. SFAs in psoriasis

Increased intake of high-fat diet (HFD)-containing SFAs is proposed to be one of the major mechanisms of obesity [8], the prevalence of which has markedly increased in most developed countries over the past two decades [9]. Various epidemiological studies have suggested a close positive association between obesity and the development of various inflammatory diseases, including psoriasis [9]. Specifically, the extent of obesity is significantly correlated with the incidence and the severity of psoriasis [10,11]. Because an increase in adipose tissues is a prominent feature of obesity, changes in cell composition in adipose tissues and increased production of adipokines from adipose tissues have the focus for mechanisms linking obesity and exacerbated inflammation in psoriasis [12]. However, recent studies indicate that SFAs, rather than obesity itself, play important roles in the exacerbation of psoriasis in the obese population.

2.1. Regulation of keratinocyte functions and inflammasome activation

Kanemaru et al [13] first reported exacerbation of psoriatic dermatitis in HFD-fed mice, although most of the data were obtained from analysis of db/db mice, which lack the leptin receptor and exhibit an obese phenotype due to uncontrolled appetite. In mice, IMQ-induced epidermal hyperplasia and mRNA expression levels of cytokines, such as IL-17 and IL-23, in the skin were significantly increased compared with those in control wild type (WT) mice. Because leptin functions as an immune regulator by affecting the functions of various immune cells [14], a lack of leptin signaling itself may also affect the development of dermatitis. Nevertheless, mice fed a HFD exhibited significantly increased ear swelling responses compared to normal diet (ND)-fed mice, suggesting that not only obesity but also dietary lipids, exacerbate psoriatic dermatitis. As a mechanism of exacerbation, the authors focused on the role of palmitic acids, a type of SFA, on keratinocyte proliferation. Application of palmitic acids in human keratinocyte culture induced regenerating islet-derived 3α (REG3A) expression, a human homolog of mouse regenerating islet-derived 3γ (Reg3γ), suggested to be involved in epidermal hyperplasia in psoriasis [15]. These results suggest that SFAs promote epidermal hyperplasia in psoriasis via induction of REG3A [13].

Activation of the inflammasome is also proposed as a mechanism of SFAs promoting psoriatic dermatitis. Vasseur et al [16] reported that mice fed a HFD exhibited epidermal activation of caspase-1 and overexpression of IL-1β, even at steady state. Because IL-1β induces expression of CCL20, a chemokine that recruits Th17 and dermal γδ T cells, a primary IL-17-producing cell in mouse skin, intake of HFD may lead to the accumulation of IL-17-producing cells in the skin and exacerbate psoriatic dermatitis. Zang et al [17] further reported more detailed mechanisms of inflammasome activation by SFAs. In their model, mice fed a HFD spontaneously developed dermatitis and exacerbated psoriatic dermatitis in the IMQ-

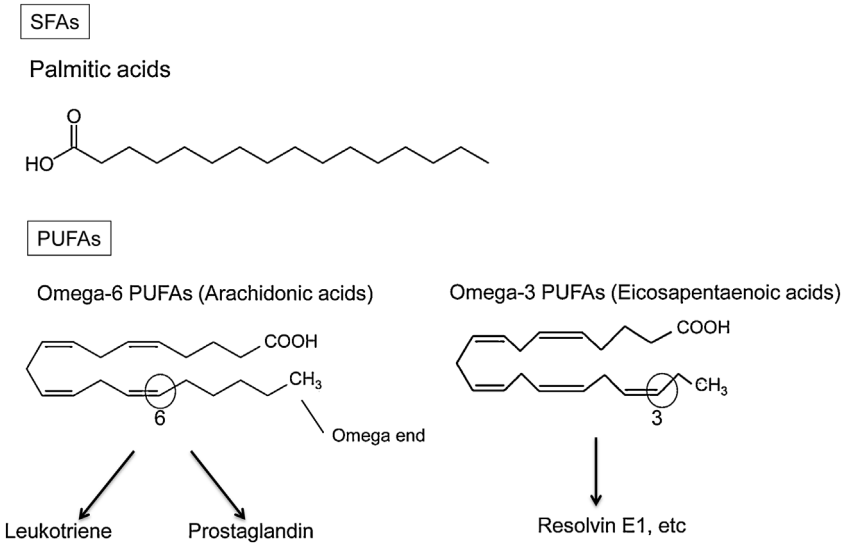

Fig. 1. Chemical structures of saturated fatty acids (SFAs: palmitic acids), omega-6 polyunsaturated fatty acids (PUFAs: arachidonic acids) and omega-3 PUFAs (eicosapentaenoic acids).

induced psoriasis model, with increased numbers of $CD11c^+$ macrophages in the epidermis and dermis. These cells produce IL-1β and IL-18 and promote IL-17-mediated dermatitis. Palmitic acids induce activation of NLRP3 and production of IL-1β and IL-18 in macrophages. In addition, expression of epidermal fatty acid binding protein (E-FABP), an intracellular chaperone coordinating lipid trafficking and biological function, was upregulated in $CD11c^+$ macrophages from HFD-fed mice. As such, they focused on the role of E-FABP in HFD-induced dermatitis, revealing that activation of the NLRP3 inflammasome pathway via E-FABP signaling mediates the production of IL-1β and IL-18 and causes exacerbated psoriatic dermatitis. Activation of caspase-1 in the skin of HFD-fed mice was reproduced by Higashi et al [18]. Collectively, these results suggest that SFAs in a HFD facilitate psoriatic dermatitis via activation of the inflammasome in the skin.

2.2. Induction of IL-17-producing cells

Intriguingly, increased accumulation of Th17 is observed in the skin in lymph nodes from HFD-fed mice [16,17], suggesting that HFD promotes proliferation or differentiation of Th17 cells. In line with these findings, facilitation of Th17-differentiation by HFD was also reported by Endo et al [19]. SFAs in HFD induce expression of acetyl CoA carboxylase (ACC1), a lipid metabolic kinase, in $CD4^+$ T cells. ACC1 modulates the DNA-binding of RORγ1, a master transcriptional factor in Th17 cells that promotes their development both in vitro and in vivo. These mechanisms may contribute to HFD-induced exacerbation of psoriatic dermatitis. We also provided evidence that HFD exacerbates IMQ-induced psoriatic dermatitis by inducing systemic increases in IL-17-producing γδ T cells (γδ T17 cells) [20]. In our system, the number of both Th17 cells and γδ T17 cells were significantly increased in the skin of HFD-fed mice, but the increase was much more prominent in γδ T17 cells. In addition, in the skin of HFD-fed mice, expression of γδ T cell-recruiting chemokines, such as CCL20 and CXCL16, was markedly elevated compared to ND-fed mice. CCL20 is primarily expressed in keratinocytes and blood endothelial cells, and SFAs induce expression of CCL20 in both keratinocytes and blood endothelial cells in vitro. These results further support the concept that SFAs in HFDs exacerbate psoriasis through multiple mechanisms.

2.3. Therapeutic potential of SFA restriction in psoriasis

Caloric restriction and weight loss improve psoriasis symptoms [21,22]. For example, a randomized controlled study evaluated the impact of dietary intervention and physical exercise on psoriasis in obese patients [21]. In the intervention group, the mean severity score was significantly improved compared to the control group, suggesting the importance of diet in the regulation of psoriasis. However, it remains unclear which factors, weight loss or diet restriction, caused the improvement in psoriasis. Using a mouse psoriasis model, Herbert et al [23] have shown that SFAs are key players in the regulation of psoriatic dermatitis independent of obesity in HFD-fed mice. The authors first confirmed exacerbation of psoriatic dermatitis in obese mice fed a HFD rich in SFAs. Intriguingly, HFD-fed mice exhibited exacerbated dermatitis even before the appearance of the obese phenotype. In contrast, an exacerbated phenotype was not observed in obese mice fed a PUFA-rich HFD. Furthermore, obese mice fed this SFA-rich HFD did not exhibit exacerbated dermatitis after switching to a ND. SFAs sensitize macrophages to increased inflammatory responses to pro-inflammatory stimuli [23]. These results strongly suggest that SFAs in HFD, rather than weight gain alone, are the cause of exacerbated psoriasis in obese patients [24]. A recent report also suggested that the combination of SFAs and sugar in HFDs is important for the exacerbation of psoriatic dermatitis in HFD-fed mice [25]. Together, these results demonstrate that regulation of SFA intake improves symptoms of psoriasis. Table 1 contains a summary of recent studies regarding the association between SFAs and psoriasis using a mouse model of psoriasis. As shown here, the phenotype of HFD-fed mice is differs depending on the studies. Distinct compositions of fatty acids in HFDs, together with various environmental factors, such as the microbiota, influence the overall effect of HFDs on psoriatic dermatitis. Fig. 2 shows proposed mechanisms of SFA-induced exacerbation of psoriasis.

3. Omega-6 PUFAs in psoriasis

Arachidonic acid, an omega-6 PUFA, is a major fatty acid that constitutes the membrane phospholipids of cells. When tissues are exposed to various stimuli, such as trauma and cytokines, arachidonic acid is released from membrane phospholipids and converted into lipid mediators by various enzymes. Prostanoids and leukotrienes (LTs) are major lipid mediators derived from arachidonic acid [26] that exert a variety of functions in multiple pathophysiological conditions [26,27]. Increases in several prostanoids and LTs have been reported in human psoriatic skin lesions [28], however, their roles in the development of psoriasis remain unclear. In this section, we discuss possible roles for omega-6 PUFA-derived lipid mediators in psoriasis as revealed by recent mouse studies, focusing on prostanoids and LTs.

3.1. Prostanoids and psoriasis

Prostanoids are formed by the cyclooxygenase (COX) pathway [27] (Supplemental Fig. 1). The COX reaction results in formation of an unstable endoperoxide intermediate, prostaglandin H_2 (PGH_2), which is subsequently metabolized to prostanoids, including PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane (TX) A_2 by specific synthases [26]. Prostanoids exert their functions through their respective receptors, all of which are G-protein-coupled rhodopsin-type receptors with seven transmembrane domains. There are nine types and subtypes of prostanoid receptors that are conserved in mammals from mice to humans: two subtypes of the PGD receptor [DP and chemoattractant receptor homologous-molecule expressed on Th2 cells CRTH2)], four subtypes of the PGE receptor (EP1, EP2, EP3 and EP4), the PGF receptor (FP), the PGI receptor (IP) and the TXA receptor (TP) [26]. Among these receptors, EP2 and TP involvement has recently been reported in psoriatic dermatitis.

To investigate whether and how prostanoids play roles in psoriatic dermatitis, we performed targeted lipidomics analysis of psoriatic lesions from the IMQ-induced psoriasis model [29]. In these lesions, TxA2 increased in parallel with dermatitis progression. TxA2 synthase is consistently upregulated in human psoriatic lesions. Next, we utilized TP-deficient mice in an IMQ-induced psoriasis model and observed that TP-deficient mice exhibited significantly impaired dermatitis with decreased γδ T17 cell numbers in the skin. TP stimulation in γδ T cells enhanced IL-23-induced IL-17 production, and WT mice treated with an inhibitor for TXA_2 synthase exhibited decreased dermatitis with impaired IL-17 production from γδ T cells in the skin [29]. Thus, TXA_2–TP signaling may facilitate psoriatic dermatitis by promoting IL-17 production in psoriatic lesions.

Other than TXA_2, PGE_2 is also a candidate prostanoid that promotes the development of psoriatic dermatitis through regulation of IL-23/Il-17 pathways. IL-23 is an essential cytokine for the development of psoriasis that acts by inducing the

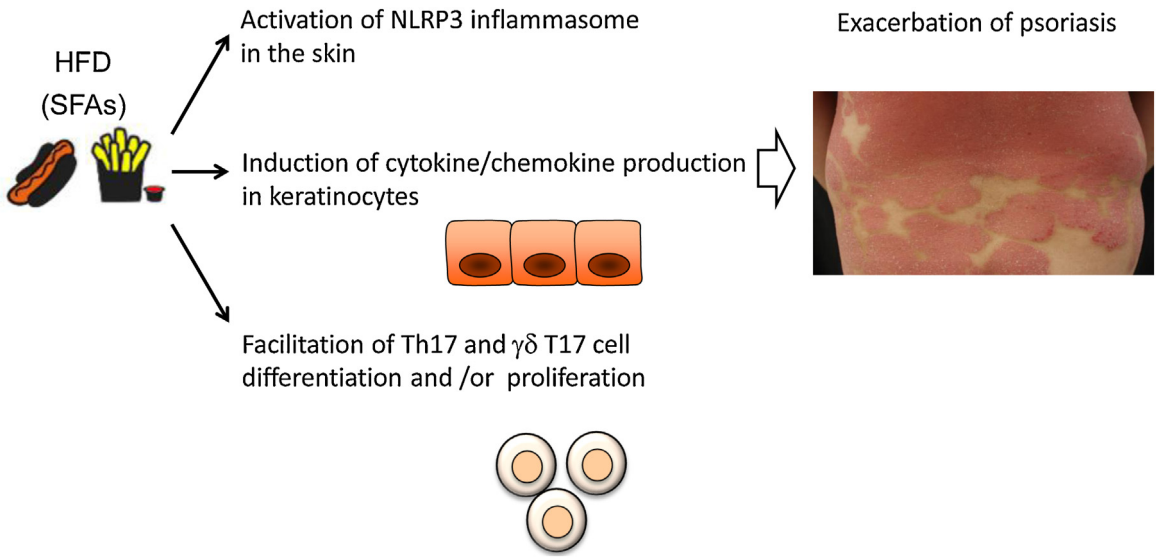

Fig. 2. Proposed mechanisms of SFA-induced exacerbation of psoriasis.

generation and activation of Th17 cells. It has previously been reported that PGE_2 produced by fibroblasts promotes IL-23 production from DCs, which support the expansion of Th17 cells in vitro [30], suggesting that PGE_2 promotes the development of psoriasis. Lee et al revealed that PGE_2 produced by Th17 cells enhances the expression of an IL-23 receptor subunit gene on Th17 cells through EP2 and EP4, facilitating the generation of Th17 cells in vitro and in vivo [31]. Combined deletion of EP2 and EP4 in T cells inhibited the accumulation of Th17 cells in the skin and abolished psoriatic dermatitis in an IL-23-induced mouse psoriasis model [31]. Therefore, inhibition of PGE_2–EP2/EP4 signaling may reduce the number of Th17 cells in psoriasis patients and represents a potential therapeutic target for psoriasis.

3.2. LTs and psoriasis

LTs are generated by the 5-, 12- and 15-lipoxygenase (LO) pathway. LTs include LTB_4 and cystenyl (Cys). Cys LTs are further classified into LTC_4, LTD_4 and LTE_4. Similar to prostanoids, LTs exert their functions through their specific G-protein-coupled receptors found on the cell surface. LTB_4 binds to two types of receptors, high-affinity BLT1 and low-affinity BLT2 [32], and Cys LTs binds to $CysLT_1$ and $CysLT_2$ [33].

Application of nonsteroidal anti-inflammatory drugs (NSAIDs) sometimes exacerbates psoriasis. NSAIDs inhibit COX activity, which diverts arachidonic acid to the lipoxygenase pathway and increases production of LTs [28]. Thus, increased LTs was postulated as a mechanism for NSAID-induced exacerbation of psoriasis, and LTs are generally considered disease-promoting factors in psoriasis. However, whether LTs are involved in psoriasis remains unknown. Sumida et al reported the essential role of LTB_4–BLT1 signaling in neutrophil infiltration in the IMQ-induced psoriasis model [34]. Neutrophil infiltration is a characteristic histological feature of psoriasis, and there are cases in which neutrophil depletion results in amelioration of clinical symptoms of psoriasis [35], suggesting a pathogenic role for neutrophils in psoriasis. In the IMQ-induced psoriasis model, BLT1-deficient mice, as well as WT mice, treated with inhibitors for LTB4 synthesis exhibit significantly impaired neutrophil infiltration in the skin and improved dermatitis scores [34]. LTB_4–BLT1 signaling in neutrophils significantly accelerates neutrophil infiltration in the skin through cooperation with CXCR2, a chemokine receptor for CXCL1/2 [34]. In contrast, one report demonstrated nonsignificant roles for LTB4-BLT1 signaling in the development of IMQ-induced psoriatic dermatitis, although the experimental protocol was slightly different than the other study, and only clinical symptoms were evaluated in this study [36]. In clinical trials using LT inhibitors for psoriasis, controversial results were obtained; some studies showed significant clinical improvement [37], while others did not [38]. Thus, the extent to which LTB4-BLT1 signaling contributes to psoriasis may differ depending on the context.

4. Omega-3 PUFAs in psoriasis

Epidemiological studies have demonstrated that individuals on diets with a high ratio of omega-3 PUFAs/omega-6 PUFAs exhibit reduced frequency and severity of psoriasis [39]. In addition, several studies have shown that administration of omega-3 PUFA-containing supplements ameliorates the degree of various inflammatory diseases, including psoriasis [40]. Thus, omega-3 PUFAs have long been suspected to have anti-psoriatic effects. Omega-3 PUFAs play anti-inflammatory roles 1) through competition with the metabolic pathways of omega-6 PUFAs and subsequent reduction of omega-6 PUFAs with pro-inflammatory properties and 2) through production of omega-3 PUFA-derived metabolites with anti-inflammatory properties [41]. Perturbation of lipid rafts, structures in the plasma membrane formed through lipid-lipid and lipid-protein interactions that optimizes the clustering of signaling proteins is also proposed as an anti-inflammatory mechanism of omega-3 PUFAs [42]. Although whether and how omega-3 PUFAs regulate the development of psoriasis remains unresolved, but several possibilities have recently been demonstrated in mouse studies.

4.1. Regulation of Th17 differentiation

FAT-1 is an enzyme that converts endogenous omega-6 PUFAs to omega-3 PUFAs. FAT-1 adds a double bond to arachidonic acid,

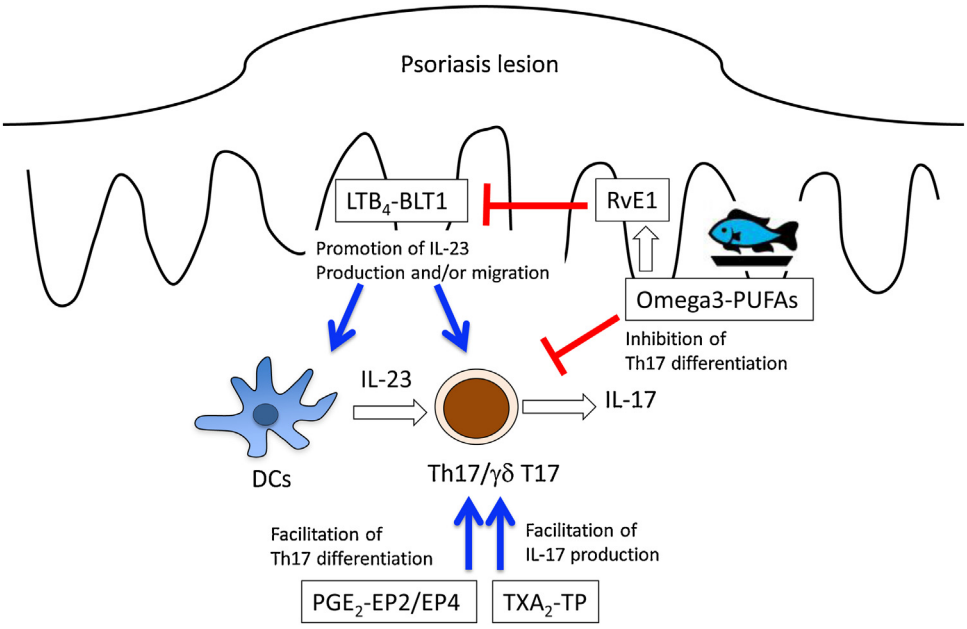

Fig. 3. Possible actions of prostanoids and omega-3 PUFAs on the development of psoriasis. LTB_4: Leukotriene B4, TxA_2: Thromboxane A_2, PGE_2: Prostaglandin E_2.

changing them into EPAs. Mice genetically engineered to express FAT-1 (FAT-1 TG mice) exhibit significantly reduced levels of Th17 cells and increased Tregs in the spleen and experience milder dermatitis in the IMQ-induced psoriasis model [43]. Th17 differentiation in FAT-1 TG mice is impaired due to reduced expression of the IL-6 receptor and reduced activation of STAT3 in CD4 + T cells, suggesting that EPAs modulate lipid rafts in CD4 + T cells and regulate the expression of IL-6 receptors [44]. Other than EPAs, DHAs are also thought to regulate Th17 differentiation. DHA-treated DCs exert a reduced ability to induce Th17 differentiation and proliferation [45]. Consistently, mice fed a DHA-rich diet exhibited reduced disease severity in an EAE model, a Th17-mediated model of inflammation [45]. These reports further suggest that omega-3 PUFAs may play protective roles against psoriatic inflammation through inhibition of Th17 differentiation.

4.2. Anti-inflammatory metabolites of omega-3 PUFAs

In addition to these mechanisms, we also identified a novel regulatory role for an omega-3 PUFA-derived lipid mediator, resolvin E1 (RvE1), in psoriatic dermatitis. RvE1 is a derivative of EPA and has two receptors: ChemR23 and BLT1, a LTB4 receptor [46]. RvE1 exerts agonistic effects on ChemR23, while mediating antagonistic functions on BLT1. The anti-inflammatory effects of RvE1 have been reported in several inflammatory disease models, such as DSS-induced colitis [47], asthma [48] and contact hypersensitivity [49]. Using an IMQ-induced psoriasis model, we evaluated the anti-inflammatory effects and the molecular mechanisms of RvE1 in psoriatic dermatitis [50]. Administration of RvE1 potently inhibited expression of IL-23 and IL-17 in the skin and suppressed the development of psoriatic dermatitis. Stimulation of DCs with LTB4 induced IL-23 production and migration of dendritic cells, which was blocked by RvE1. LTB4 also facilitates migration of γδ T17 and Th17 cells in humans, which was abrogated by RvE1. These results suggest that RvE1 exerts anti-psoriatic functions through regulation of DC and γδ T cell functions by blocking LTB4-BLT1 signaling [50]. Collectively, omega-3 PUFAs may play suppress psoriasis through multiple mechanisms (Fig. 3).

5. Conclusions

Herein, we summarized current findings on the potential actions of dietary lipids in psoriasis. Dietary lipids have the potential to promote or suppress the development of psoriasis, and the underlying mechanisms are gradually being revealed. Currently, biologics targeting cytokines, such as IL-23 and IL-17, are widely used for the treatment of psoriasis and have dramatically changed therapeutic strategies for this disease. However, biologics possess several critical problems, such as an increased risk for infection, potential negative effects on tumor progression, and high economic burden. Manipulation of dairy intake of dietary lipids or targeting dietary lipids as therapeutic targets may represent a safer and more cost-efficient treatment option for psoriasis, overcoming the issues of treatment with biologics. In addition, analysis of psoriasis pathophysiology from the perspective of dietary lipids may facilitate discovery of novel pathological mechanisms in psoriasis.

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Conflicts of interest statement

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2019.05.003.

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