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NOVELTIES IN DERMATOLOGY

Lipid Nutrition and the Epidermal Barrier: The Connection Between Immune-Mediated Inflammatory Diseases and Peroxisome Proliferator-Activated Receptors, a New Therapeutic Target in Psoriasis and Atopic Dermatitis

V.G. Villarrubia,[a,*] S. Vidal-Asensi,[b] V. Pérez-Bañasco,[c] J. Cuevas-Santos,[d] and R. Cisterna-Cáncer[e]

[a]*Departamento de I+D+i, Inmunología, Bioaveda, Jaén, Spain*
[b]*Servicio de Dermatología, Hospital Gómez-Ulla, Madrid, Spain*
[c]*Servicio de Nefrología, Hospital de Jaén, Jaén, Spain*
[d]*Servicio de Patología, Hospital de Guadalajara, Guadalajara, Spain*
[e]*Departamento de Inmunología, Microbiología y Parasitología, Facultad de Medicina, Universidad del País Vasco, Bilbao, Spain*

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Olive oils

Abstract
The authors describe peroxisome proliferator-activated receptor (PPAR) transcription factors as connectors between the enzymatic mechanisms of the epidermal barrier and the abnormal immune and inflammatory responses that characterize atopic dermatitis and psoriasis. Also described is a new connection between lipid metabolism and the epidermal barrier. A suggestion that emerges is that atopic dermatitis and psoriasis share at least 2 pathogenic mechanisms-namely, deficient expression of PPAR-α and impaired production of interleukin-10 and interferon-γ-in spite of differences in causes and manifestations. A standardized olive oil formulation with powerful bactericidal and fungicidal effects also has the ability to increase serum levels of these 2 cytokines and regulate serum levels of high-density lipoprotein cholesterol in patients at high risk for inflammatory and cardiovascular disease, suggesting that these may be among the mechanisms responsible for the benefits observed following oral and/or topical administration in patients with atopic dermatitis or psoriasis.

*Corresponding author.
E-mail address: villarrubia@bioaveda.com (V.G. Villarrubia).

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PALABRAS CLAVE
Dermatitis atópica;
Psoriasis;
PPAR;
Barrera epidérmica;
IL-10/IFN-γ;
Aceites de oliva

Barrera epidérmica y nutrición lipídica. La conexión PPAR e inmunopatología inflamatoria como nuevas dianas de tratamiento en dermatitis atópica y psoriasis

Resumen
Los autores describen los factores peroxisome proliferator-activated receptors (PPAR) como conectores entre los mecanismos enzimáticos de la barrera epidérmica (BE) y las alteraciones inmuno/inflamatorias que caracterizan a dermatitis atópica (DA) y psoriasis. Igualmente, se describe una nueva conexión entre el metabolismo lipídico y la BE. El análisis de estos hechos permite sugerir que DA y psoriasis, aunque diferentes en su causalidad y clínica, exhiben al menos dos hechos patogénicos comunes, que se manifiestan por defectos en la expresión de PPAR-α y en la producción de IL-10 e IFN-γ. La capacidad de una formulación magistral de aceites de oliva (FMAO) para aumentar los niveles séricos de ambas citocinas, y regular el colesterol HDL sérico, en pacientes con alto riesgo inflamatorio/cardiovascular, junto a sus potentes efectos bactericidas y fungicidas, sugiere que estos sean algunos de los mecanismos responsables de los positivos efectos observados con la FMAO (oral y/o tópica) en pacientes con DA y psoriasis.

Introduction

In an earlier review, we explained how changes to the epidermal barrier were largely due to events related to filaggrin function.[1] However, given that mutations in the genes encoding this protein are present in only 15%-20% of patients with atopic dermatitis,[2,3] we suggested that the remaining cases are due either to mutations—with subsequent functional impairment—in the genes that encode some of the enzymes implicated in the mechanism of filaggrin activation or to other epiphenomena that suppress the action of these enzymes, leading to similar changes in the epidermal barrier.[1] According to this enzyme-based theory, fatty acid-binding proteins (FABP) would play a crucial role, enabling certain enzymatic actions in the intestine and skin through the transport of dietary fatty substrates to the cell membranes (Figure 1).[1]

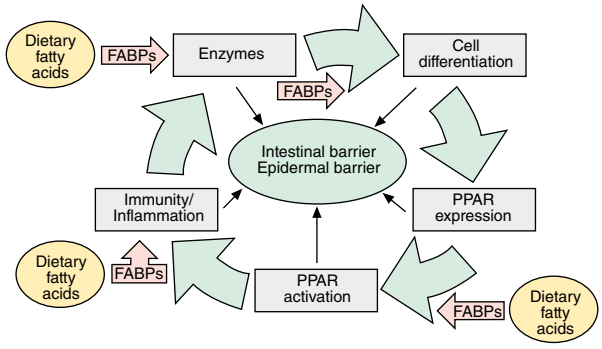

Figure 1 Nosological aspects of the mechanisms common to the formation and maintenance of both the intestinal barrier and the epidermal barrier: the "food → fatty acids → enzymes → PPAR (FFEP)" pathway. See text. FA indicates fatty acids; FABP, fatty acid-binding proteins; PPAR, peroxisome proliferator-activated receptors.

In an organ as complex as the human skin seems to be, this ordered interaction of players (profilaggrin, filaggrin, lipoxygenase [LOX] enzymes, caspases, matriptase, etc, along with the FABP transporters), which influences cell differentiation in the epidermal barrier (Figure 1), has evolved to provide appropriate defense mechanisms against internal and external insult.[1] This complexity stands in contrast to the crude simplicity of the skin of some of our more distant ancestors-fish and birds. In this evolution-based framework, the term ichthyosis, or fish scale disease, is appropriate in pathogenic terms.

In the regulatory mechanisms of all these epidermal constituents and in the pathogenesis of disorders involving them, of note is the almost ubiquitous presence of peroxisome proliferator-activated receptors (PPARs), as well as the involvement of certain immune/inflammatory mechanisms that are still not fully understood (Figure 1). These molecules and mechanisms will be the subject of this review.

Intestinal and Epidermal Barriers: Nutrition, PPAR, and the Skin

Today, it is clear that nutrition may have beneficial or detrimental effects for the organism through its impact on the expression of different host genes. Different levels of expression are achieved through activation or suppression of different specific transcription factors.[4,5] The most important group of factors is a special set of nuclear receptors 1, known as PPAR, that mediate the endogenous effects of dietary fatty acids.[6-8] For regulation of transcription by PPAR to occur, these molecules must have formed a heterodimer with the retinoid X receptor (RXR).[6] Once activated by the corresponding agonist, the PPAR/RXR heterodimer promotes transcription by binding to peroxisome proliferator-response elements present in and close to the promotor sequence of the target genes.

Currently, the 3 PPAR isotypes that have been identified are denoted α, β/δ, and γ. Some of their characteristics

Table 1 Characteristics, Functions, and Dietary Lipid Agonists of PPAR-a Nuclear Factors in the Intestine

Location and Function	PPAR-α Agonists
Small intestine: Differentiated enterocytes[8] ↑ β-oxidation FAs[10]: ↓ intestinal inflammation[11] ↓ Cholesterol uptake and ↑ transfer to Apo-A1 (HDL-C)[10] ↓ Amino acid absorption and ↑ intestinal motility[10] ↓ effects of oxidative stress[10] ↓ signaling pathway for IL-17 and EGFR[8] *Skin:* Differentiated enterocytes[14,15] Fetal skin development[15] Maturation of epidermal barrier: keratinocyte differentiation[24-26] Repair of traumatic skin insult[15] Decreased migration of melanoma cells[14] Increased sebum production (acne?)[21] Decrease in atopic dermatitis, psoriasis, actinic keratosis, and squamous cell carcinoma[14,22]	*Fatty acids[10]:* • MUFA: oleic acid[28 a] • PUFA: linoleic acid[a] and AA,[24] EPA, and DHA *Fatty acid derivatives:* • Due to 12/15 LOX actions on linoleic acid and AA: LTB4, 5 and 8 *S*-HETEs[1,24,25] • Derived from oleic: OEA[30] • Derived from saturated fats (palmitic): PEA[32]

Abbreviations: A, arachidonic acid; Apo-A1, apolipoprotein A1; DHA, docosahexaenoic acid; EGFR, epidermal growth factor receptor; EPA, eicosapentaenoic acid; HDL-c; high density lipoprotein cholesterol; IL-17, interleukin 17 (proinflammatory); LBT4, leukotriene B4; MUFA, monounsaturated fatty acids (oleic acid: principal component of olive oil); OEA, oleoylethanolamide; PEA, palmitoylethanolamide; PUFA, polyunsaturated fatty acids; 12/15 LOX, 12/12 lipoxygenases.

[a]The principal constituents of olive oil (though with qualitative and quantitative differences in different oils).

will be described in this article, but given our specific concerns for the purposes of this review, we will only analyze PPAR isotypes present in the small intestine and the skin, with special reference to the most ubiquitous of all, PPAR-α (Table 1).

We should point out here that, as is the case for other cutaneous and systemic enzymes analyzed by our group,[1] the biological importance of PPAR-α is largely due to its almost ancestral presence in the mechanisms involved in the evolution of the species. Indeed, PPARs are present in evolutionary segments prior to the emergence of animals.[9] In these species, the mechanisms of activation by oleic acid (the fundamental constituent of oil from olives and other plants) are similar to those that occur in humans.[9] This gives a fairly precise idea of the importance of these fatty acids in fat nutrition as a partial support for phylogenetic life. It also suggests that olives, and other fatty-acid-producing plants, were present in remote evolutionary time.

PPARs and the Intestinal Barrier

PPAR-α isotypes are mainly expressed in differentiated enterocytes in the small intestine.[10] They are therefore exposed to high levels of dietary lipid agonists: primarily monoglycerides and fatty acids (and their derivatives), produced from the digestive hydrolysis of dietary triglycerides prior to entry into the enterocytes.[11] The role of PPAR-α in the expression of genes that control the intestinal barrier (responsible for the transport of proteins and phase I/II enzymes) has been reported recently in studies that have investigated the actions of some of the most widespread fatty acids in the diet. Thus PPAR-α activation in differentiated enterocytes plays a part in a whole range of activities[12] (Table 1). First, PPAR-α participates in the regulation of catabolism of the fatty acids through different absorption mechanisms. Oxidation subsequently occurs in the mitochondria and peroxisomes. PPAR-α also participates in ω-oxidation of fatty acids and the generation of energy substrates for glycogenolysis and the Krebs cycle. (We should remember that intestinal FABP [FABP-I] is partly responsible for the transport of dietary fatty acids to the PPARs.[1]) Given that β-oxidation of the fatty acids is associated with less severe inflammatory bowel disease,[13] dietary activation of PPAR-α could be important in the treatment of this disease and other similar immune system and inflammatory disorders, such as certain skin diseases (allergic dermatitis and psoriasis, as we shall see). Second, PPAR-α activation contributes to reducing the effects of oxidative stress through the promotion of a range of genes involved in endogenous antioxidant defense mechanisms. The positive effects of fatty acids with respect to oxidative processes can be explained by bearing in mind that oxidative stress results in increased cell damage and apoptotic phenomena,[14] and that PPAR-α activation by a number of agonists[12] also leads

to suppression of proapoptotic genes (such as those that encode caspase-3).[10] Finally, PPAR-α activation suppresses the expression of epidermal growth factor receptor (EGFR) and the activation of the signaling pathway for interleukin (IL) 17 and for the inflammatory response,[10] among other events of particular relevance for this topic (Table 1).

As in the digestive tract and other tissues that express PPAR-α, the ultimate aim of activation of this skin receptor is to block the cells in transition from phase G1 to S of the cell cycle, thereby reducing proliferation and increasing differentiation while regulating lipid metabolism and the cellular energy balance[8,15] in addition to other inflammatory and immune responses that we shall discuss later. These findings support the suggestion that FABP-I is responsible for transporting dietary fatty acids to intestinal PPAR-α.[1] They also give an indication of the importance of monounsaturated fatty acids (oleic acid) and polyunsaturated fatty acids (linoleic, linolenic, and arachidonic acids) (Table 1)—all of which are essential components of olive oil—in nutrition and systemic biologic homeostasis of vertebrates.

PPARs and the Epidermal Barrier

The presence of PPAR nuclear factors in the skin is unquestioned nowadays. As in the digestive tract, these factors regulate cell proliferation (inhibition) and differentiation (activation) phenomena, and also exercise a negative control over inflammatory response.[16] The cell target changes: in the skin it is the keratinocytes rather than enterocytes, as in the digestive tract. Nevertheless, keratinocytes have already undergone differentiation through enzymatic processes described elsewhere (Figure 1).[1] The similarity of physiological and pathological situations in the intestinal and epidermal barriers provides, as we shall see, strong support for the argument that diet has an overwhelming influence on the structure and functionality of the skin, thereby explaining part of the therapeutic effects already described,[1] in addition to the ones we shall describe later.

The 3 isotypes of PPAR are expressed in physiological conditions, both in murine and human skin; PPAR-α is implicated in functions related to the development of fetal skin development, maturation of the epidermal barrier, and sebaceous cell activity (Table 1).[17] PPAR-β/δ regulates the differentiation of sebaceous cells, promotes hair follicle growth, and exhibits prodifferentiating effects on keratinocytes, both in physiological and inflammatory conditions. In addition, both factors are considered as essential for repair after a variety of different skin insults. In contrast, some authors suggest that PPAR-γ might not play an important direct role in keratinocytes (see later), although PPAR-γ does participate in the differentiation of sebaceous glands.[17] (For more detailed information on cutaneous regulation processes other than those involving PPAR, see reference 18.)

Although these appear to be the physiological roles of PPARs, progress in the study of these factors in different skin diseases is highlighting the specific role of each isotype and new biological functions are being discovered. Thus, expression of PPAR-α is downregulated in hyperproliferative processes such as psoriasis, as well as in patients with diseases such as atopic dermatitis, actinic keratosis, and squamous cell carcinoma of the skin (Table 1). In actinic keratosis and squamous cell carcinoma, expression of PPAR-β/δ is also upregulated.[16] These findings are in agreement with the recent function ascribed to PPAR-β/δ, specifically that activation of these factors by ceramides leads to overexpression of the adenosine triphosphate binding cassette transporter, family 12.[19] This promotes deposition of glucosylceramides in lamellar bodies of the keratinocytes, thereby contributing to the formation of the epidermal barrier. The importance of this event can be understood if we bear in mind the lipid abnormalities in atopic dermatitis, characterized by decreased levels of some ceramides[20] and fatty acids (such as oleic acid),[21] leading to the lipid and water loss characteristic of this disease.[22]

Similarly, some new treatments have demonstrated the crucial role of PPAR factors in the pathogenesis of different skin diseases. Thus, all PPARs—when activated by their specific agonists or pan-agonists—increase the production of sebum both in vitro and in vivo in humans.[23] This suggests that caution should be exercised when targeting PPAR in patients with acne (Table 1). Expression of PPAR-α is reduced in experimental models and in patients with atopic dermatitis.[24] Topical application of a specific agonist for this receptor reduces antigen-induced inflammation in animal models. Interestingly, oral administration of PPAR-γ agonists also reduces the clinical symptoms in patients with atopic dermatitis,[25] thereby providing further evidence of its involvement in the pathogenesis of the disease. In fact, it seems that the regulatory effects of PPAR-γ on inflammation also help maintain the homeostasis of the epidermal barrier.[25] Other authors do indeed report that PPAR-γ can induce keratinocyte differentiation,[26-28] although not to the same extent as PPAR-α, activated endogenously by 8S-hydroxy-eicosatetraenoic acid derived from the actions of 12/15 LOX on arachidonic and linoleic acid (Table 1),[1,26,27] both of which are components of olive oil. As can be deduced, these phenomena once again suggest that a physiological pathway of fatty acids → enzymes (LOX) → PPAR is present, as we have reported (Figure 1).[1]

Finally, we have seen that PPAR-α activation is also beneficial in models of irritative and allergic contact dermatitis,[29] which are occasionally present alongside atopic dermatitis or show similar immunopathogenic events. In addition, dietary fat ensures expression of FABP and PPAR-α in nursing infants[1,30]—reflecting the importance of breast milk in preventing diseases, including skin diseases[31]—and stimulates mobilization of lipid mediators that control sensation of fullness in the duodenum-jejunum. Of these dietary fats, of note are oleoylethanolamide (OEA) and other fatty acid ethanolamides (FAE), but not saturated fatty acids (for example, palmitoylethanolamide [PEA]).[32,33] Interestingly, OEA—a natural derivative of oleic acid-behaves like a potent specific agonist of PPAR-α factors in the small intestine,[34] whereas PEA—a natural derivative of palmitic acid (saturated)-acts in the skin as a potent endogenous anti-inflammatory and antiallergic

agent through activation of the PPAR-α pathway.[35] Given that activation of PPAR-α by oleic acid is also accompanied by increased intestinal motility,[12] these experimental observations correspond to the positive clinical effects of an extemporaneous preparation of olive oil on constipation observed by our group in patients with chronic renal disease[36] and elderly patients.[37] Other positive properties include the potent immune system effects that regulate high-density lipoprotein (HDL) cholesterol and exhibit microbicidal properties, as will be seen at the end of this article. But do these observations provide clear evidence for a complete physiological pathway of Food → fatty acids → FABP → Enzymes (LOX) → PPAR (the FFEP pathway in fig. 1). Such a pathway, which is present in both the intestinal and epidermal barriers, would provide scientific evidence for a link between diet and skin health.

In summary, the positive effects of nutrition on the skin—claimed for a wide range of compounds[38] and with a rational evidence base in the case of some olive oils[39-41]—may be understood in scientific terms in view of the actions of fatty acids and other nutrients on the FFEP pathway (Table 1 and Figure 1). Clearly, though, critical analysis of all the PPAR models described to date reveals many gaps in knowledge. Thus we know that PPARs are not absolutely essential for complete epidermal maturation and renewal, and that other mechanisms may also be operating[18] (although these are beyond the scope of this article), thereby explaining why we observe other enzymatic processes.[1] In any case, it now seems established that PPARs accelerate keratinocyte differentiation and recovery of the epidermal barrier after different exogenous and endogenous insults,[17,42] as is the case in atopic dermatitis and psoriasis. PPARs also participate in the control of some of the immune and inflammatory mechanisms that we will see below.

Finally, without doubt, many compounds present in food today may play a detrimental role in the FFEP pathway. For example, the lipophilic character of many pesticides which are used as phytosanitary products[43,44] is responsible for their participation in some of the aforementioned mechanisms, essentially in the activation of PPAR,[45] proapoptotic caspases,[46] and/or estrogen receptors in breast and ovarian cancer.[47] Such events may be responsible for certain severe endocrine disorders[48,49] and skin disorders.[50-59] Furthermore, most of these products behave as potent proinflammatory agents,[43,46] suggesting possible interference in a range of immunological mechanisms that we will describe here in atopic dermatitis and psoriasis.

Immunopathogenesis and the Epidermal Barrier

The Physiology of the Immune System With Emphasis on Pathophysiology and its Modulation

The polarization of the immune system towards cell-based responses (mediated by T helper [Th] 1 cells) or humoral responses (coordinated by Th2 cells), is currently unchallenged.[60-63] Recently, a third type of immune response of a proinflammatory nature-denominated the

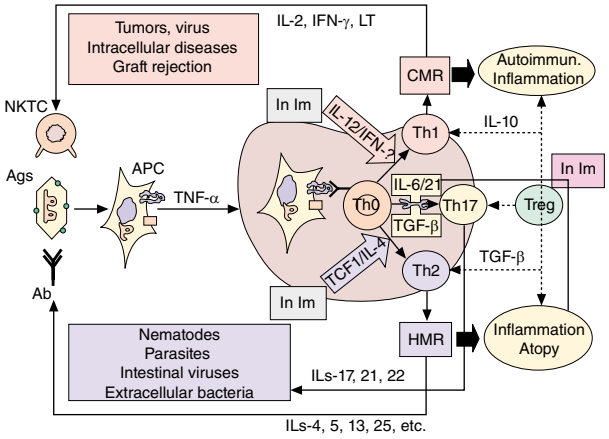

Figure 2 Immune responses and their pathogenic implications. See text. Ab indicates antibodies; Ag, antigens; APC, antigen-presenting cells; CMR, cell-mediated response; HMR, humoral-mediated response; In im, innate immunity; IFN-γ: interferon γ; IL, interleukins; LT, lymphotoxin; NKTC, (CD8+) natural killer T cells; TCF1, T-cell factor 1; TGF-β, T cell growth factor β; Th, T helper cells; TNF-α, tumor necrosis factor α; Treg, T regulatory cells. Arrows with dotted lines indicate suppression.

Th17 response-has been described.[64] From the functional standpoint (Figure 2), it is now well established that antigen-presenting cells (APC), essentially dendritic cells, capture, process, and transport antigens through the action of tumor necrosis factor (TNF)-α and other chemotactic factors to the areas of the lymphatic system into which the lesioned area drains (generally lymph nodes), in order to present the antigens to the naive $CD4^+$ T or Th0 cells.[60-63] Once activated by antigens, and in the presence of the major histocompatibility complex class II (MHC class II) and certain costimulatory molecules (Figure 2), the Th0 cells may acquire any one of at least 4 different phenotypes. Three of them are effectors (Th1, Th2, and Th17 cells) and the fourth is a regulatory compartment comprising different lymphocyte subpopulations in which the T regulatory cells (Treg) are particularly well represented.[63,65-67] The presence of these cells was initially described by some members of our group in an experimental tumor model.[68]

Among the many molecules that influence this differentiation, the cytokines produced by the APC or by auxiliary cells present in what used to be denoted the antigen presentation environment (APE), coordinated by innate immune mechanisms,[61,67,69-71] are crucial for explaining both proliferation and restriction to a particular cell subtype.[60-76] Thus, as shown in Figure 2, IL-12 and interferon (IFN) γ polarize the immune response towards Th1; T cell factor 1 and IL-4 promote development towards Th2; and IL-6 and transforming growth factor β (TGFβ), in the absence of Th1 and Th2 cells, induce a shift towards the Th17 phenotype. Likewise, as also shown in Figure 2, it seems that IL-21 can act in place of IL-6 to achieve differentiation and amplification of Th17 cells,

which are finally stabilized by the action of IL-23.[67,77] In these activities, therefore, the presence innate immune mechanisms in APE (Figure 2) mediated by IL-12- or IL-6-producing and TNF-α-producing macrophages, and by different types of IFN-γ-or IL-21-producing natural killer cells, play a crucial role in the mechanisms for polarization of the immune response.[61,67-71,75-77]

Although most inflammatory cells involved in the APE are macrophages, some of our group have described the role of mastocytes in the pathogenesis of atopic asthma.[70] Mastocytes are also present in the cutaneous immune response after exposure to UV radiation[78-80] or infection with human papilloma virus.[80] More recently, it has been shown that these cells play a very specific role in immune response by abrogating the suppressor mechanisms of the Treg cells. Thus, mastocytes producing IL-6 in abundance —in the absence of Th1 or Th2 cytokines—guide Treg and T effector cells towards IL-17-producing T cells,[81] thereby potentiating inflammation. In contrast, mastocytes can also activate Treg cells, leading to tolerance.[82] This gives an idea of the importance of these cells, and the immunological complexity that we are dealing with.

This regulation of the differentiation by cytokines of the 3 cell types is mediated by the corresponding transcription factors denoted T-bet,[83] GATA-3,[84] and RORγt,[85] with the factor FOXP3 responsible for Treg cells.[86] FOXP3—which is naturally induced during thymic differentiation of Treg cells[67] or peripherally in the presence of TGF-β and retinoic acid[87]—is inhibited by IL-6 resulting in definitive polarization towards Th17. This process suggests that the endogenous balance between the FOXP3 and RORγt functions determines the type of immune response.[86] Expression of these genes can therefore be used to study the therapeutic effect of different immunomodulators. One such case is retinoic acid, which behaves as a natural inducer of FOXP3 and an inhibitor of IL-6 and IL-23 receptors, thereby inhibiting Th17 inflammatory response through suppression mechanisms mediated by Treg cells.[88]

Once activated, Th1 cells are known to produce IFN-γ and lymphotoxin, which together with IL-2, are responsible for initiating a cell-mediated immune response. The defensive actions of this response are summarized in Figure 2. Th2 cells segregate IL-4, IL-5, IL-13, and IL-25, among other IL molecules, all of which are essential for proper generation of antibodies for the effector functions described in Figure 2. Finally, Th17 cells produce IL-17, IL-21, and IL-22. Their physiological purpose is to participate in the destruction of extracellular bacteria,[67,77] or, in a concerted action with Th1 cells, in a hypothesized resistance to certain tumors.[67,89] As is also shown in figure 2, disruption of any immune pathways leads to Th1 autoimmunity and inflammation[60,61,67,69]; Th2 atopy and inflammatory conditions,[60,61,67,70] including intrinsic aging[69,70] and skin damage due to UV[79,80] or human papilloma virus[80]; or to redundant autoimmune mechanisms, atopy, and Th17 inflammation.[63-67,77]

We should note that there are still many gaps in our basic understanding of immune response in physiological conditions. Many of these gaps are revealed by the pathogenic study of certain diseases or, by chance, on using new treatments. Thus, we have just seen such an example for retinoic acid, and we also saw something similar for some antidiabetic glitazones and certain fatty acids for the treatment of skin conditions such as atopic dermatitis and psoriasis.[1] A ready example of this difficulty is that, in physiological conditions, Th1 and Th2 cells are present in abundance but Th17 cells are scarce, and this makes them hard to study.[67] It is therefore difficult to accept that blockade and stimulation of this cell or that cell and/or cytokine might lead to obvious therapeutic outcomes, more so if we remember that most of our knowledge of these mechanisms comes from experiments with mice, whose immune system differs to a certain extent from that of humans and so inferences based on these models might not be applicable to humans.[90] Fortunately, the canine model of atopic dermatitis has a similar gene expression[91] and pathological profile[92] to humans, and studies by our group have had certain success with our extemporaneous preparation of olive oil (data not shown). Other authors have also had success through use of specific immunotherapy in these animals.[93] Second, it is clear that some regulatory factors work both ways, as is the case with TGF-β in the case of Treg cells and Th17 cells in another example of apparent biological chaos.[66,67] Thus, an approach to therapeutic development that works backwards—that is, getting the results first rather than asking more probing questions about the whys and wherefores—is important and more so in the case of nutrition, where the possibility of serious side effects is logically remote.

In any case, the situation presented—valid from the nosological point of view—is simplistic (Figure 2) in that there are many mechanisms that regulate immune response, including the involvement of the widely characterized traditional costimulatory molecules such as CD28, CD80, and CD86, and Toll receptors in innate immunity. But for the purposes of this review, we only highlight the action of the so-called Notch ligands. These are membrane receptors that, in addition to regulating immune response,[94,95] also play a substantial role in determining the fate of many cell lines, including skin cell lines.[96] Thus, Notch signals, along with transcription factors such as the PPAR-α described above, control differentiation of epidermal cells.[18] The specific depletion of Notch in keratinocytes therefore interferes with epidermal physiological differentiation, leading to severe impairment of the epidermal barrier[97,98] and lethal neonatal B cell lymphoproliferative processes due to overproduction and systemic expression of thymic stromal lymphopoietin (TSLP) by keratinocytes unable to differentiate.[97] TSLP, often used as biomarker for epidermal barrier impairment, is an IL-7-like cytokine that is also implicated in the pathogenesis of asthma and atopic dermatitis.[98-101] It can be detected as long as impairment of the epidermal barrier persists.[97] (See below and Figure 3.) Given that TSLP can activate dendritic cells[102] and T cells,[103,104] some authors have speculated that high levels of TSLP can sensitize these cells to subsequent allergen challenge in the lung.[105,106] It is important to highlight that TSLP levels are also elevated in psoriatic lesions,[107] although there is no evidence linking psoriasis with a predisposition to asthma. This phenomenon can be explained by the fact that, unlike atopic dermatitis, the predominant immune

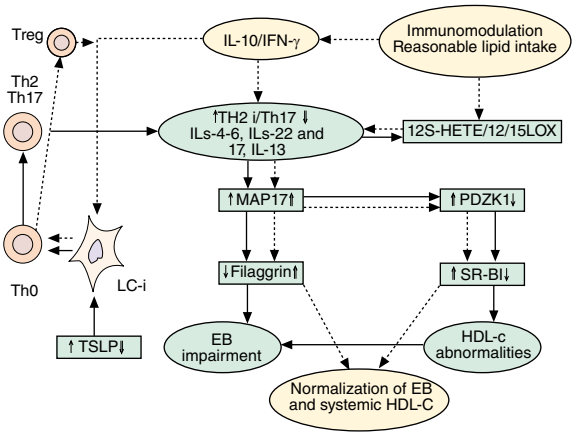

Figure 3 Implications of Th immune response in epidermal barrier disruptions and the maintenance of the Th2/Th17 inflammatory pathway and suppression of the antiinflammatory pathway mediated by Treg-IL-10 cells. Repercussions for lipid metabolism. See text. EB indicates epidermal barrier; HDL-c, high-density lipoprotein cholesterol; IFN-g, interferon γ; IL: interleukins; LC-I, proinflammatory epidermal Langerhans cells; MAP17, membrane-associated protein 17; PDZK1, gene located in the same region of chromosome 1q21 associated with atopic dermatitis; Th, T helper cells; Treg, T regulatory cells; TSLP, thymic stromal lymphopoietin.

cells in psoriasis are Th1 cells, which do not respond to TSLP.[107]

Immunopathogenesis in the Epidermal Barrier and Therapeutic Approaches

In this complex immunological context, atopic dermatitis is characterized by the predominance of the Th2 pathway and, to the lesser extent, the Th17 pathway (Table 2).[2,3,108-113] The predominance of Th2 cells (with increased IL-4 and IL-13 levels and decreased IFN-γ levels) occurs even in unaffected skin in patients with atopic dermatitis. These abnormalities are more pronounced in the lesions in which IL-5 and IL-11 (profibrotic elements) are preesnt,[108] and there are marked decreases in IL-12 expression.[108] Recent findings, however, suggest that progression of atopic dermatitis toward chronic eczematous lesions is characterized by a progressive shift towards Th1.[2,113] Often, both forms of cell expression are present at the same time (Table 2). Currently, the causes of this immune shift toward a phenotype similar to that of psoriasis are not known.

Although numerous immune conditions have been described both in atopic dermatitis and psoriasis, recent findings (Table 2) have shown the following. First, the Th17-IL-23 pathway is strongly expressed in psoriasis, and more weakly or even not at all in the acute phase of atopic dermatitis,[114] thereby explaining the incidence of recurrent infections caused by extracellular bacteria in atopic dermatitis.[110] Second, when different subpopulations of peripheral blood T cells are analyzed, there are no differences between atopic dermatitis and psoriasis,[115] although when the skin of patients with atopic dermatitis is analyzed, there is lower expression of IL-17, IL-23, and IFNγ.[110] Third, the cellular phenotype in psoriatic skin is, therefore, Th1/Th17, while that in chronic atopic dermatitis is essentially of the Th2 type, along with weak expression of Th1/Th17.[114] Fourth, there are larger subpopulations of IL-22-producing cells ($CD4^+$ and $CD8^+$) in the skin of patients with chronic atopic dermatitis than in those with psoriasis and, moreover, the number of $CD8^+$ $IL\text{-}22^+$ cells directly correlates with the severity of atopic dermatitis.[114] However, this apparently new $IL\text{-}22^+$ cell population requires further investigation. Fifth, Th17 levels in blood correlate with the severity of atopic dermatitis.[111] Sixth, infiltration of the papillary dermis by $T17^+$ cells in atopic dermatitis is more extensive during the acute phase than the chronic phase.[111] Finally, stimulation of keratinocytes by IL-17 gives rise to production of granulocyte-macrophage colony stimulating factor, IL-1, and IL-8, TNF-α, and other cell adhesion factors[111] traditionally reported in patients with atopic dermatitis.[108,115] Other characteristics are summarized in Table 2.

With regard to the initiator role of the APC, we remember that in physiological conditions, the skin contains at least 3 populations of dendritic cells: epidermal Langerhans cells, myeloid and monocyte-derived dendritic cells, and plasmacytoid-derived dendritic cells. In patients with atopic dermatitis and psoriasis, there is a fourth type denoted inflammatory dendritic epidermal cells (IDEC), with typical proinflammatory characteristics.[116-118] Functionally, it seems that the myeloid and monocyte-derived dendritic cells in atopic dermatitis express at least 2 phenotypes in blood and skin bearing an ε receptor with a high affinity for immunoglobulin (Ig) E (FcεRI). This could explain in part the biphasic (chronic and acute) nature of the disease (Table 1) as some are FεRI-expressing Langerhans cells present in the initial moments of atopic dermatitis, and the others are IDEC, which also express FcεRI and are found in the chronic phase.[116] In contrast, plasmacytoid dendritic cells—which also express RcεRI and which are crucial in IgE-mediated antiviral defense mechanisms—are almost absent from lesions of patients with atopic dermatitis.[116] Therefore, it is thought that atopic dermatitis is characterized in its initial phases by the action of Langerhans cells, in that IDEC participate in the chronic phase of the disease, as they are detected both in the epidermis and the dermis of affected subjects (Table 2).[117,118] This cell-based scenario has a number of implications. First, it allows atopic dermatitis and psoriasis to be distinguished,[110,118] as it is thought that the pathogenesis of psoriasis is due to plasmacytoid-derived dendritic cells, although perpetuation is maintained by myeloid-derived IDEC but with different markers that, in an appropriate APE (Figure 2), lead to a different immune polarization (Th1) to atopic dermatitis (Th2).[118] Second, atopic dermatitis is characterized from the start by the almost complete absence of epidermal plasmacytoid-derived dendritic cells,[116] whereas these cells are predominant in psoriasis (Table 2). Finally, in our opinion, this cell-based scenario is similar to what occurs in the peritoneal cavity under the influence of 12/15 lipoxygenase (12/15 LOX).[119]

Table 2 Immunological Characteristics of Atopic Dermatitis and Psoriasis

Characteristic	Atopic Dermatitis		Psoriasis
	Acute Phase	Chronic Phase	
Predominant Immune Response	*Th2*	*Th2/ Th1*	*Th1*
↓ *Tregs-IL-10*	↑↑ Th17-IL-23	↑ Th17-IL-23	↑↑↑ Th17-IL-23
	↓ *Tregs-IL-10*	↓ *Tregs-IL-10*	↓ *Tregs-IL-10*
APC:			
LC (mDC)	+ + +	+	↑↑↑
pDC	$^{-116}$ or $^{+107}$	$^{-116}$ or $^{+107}$	+ + + (onset)
IDEC[a]	+	+ + +	+ + + (maintenance)
Cytokine Profile:	↑ IL-4/5/13 and TNF-α	↑↑ IL-4/5/13 and TNF-α	
	↓ IL-10 and IL-12/IFN-γ	↑ IL-12/IFN-γ, CSF-GM, IL-11	
↓ IL-10	↓ IL-10 and ↑ IFN-γ (115)		
Other markers:			
PPAR-α	↓[24]	↓[24]	↓
12/15 LOX[b]	n.d	n.d	n.d
Ceramides	↓	↓	↓
FAs (oleic)	↓	↓	↓
TSLP	↑	↑↑↑ (local and systemic)	↑↑↑ (systemic)
Filaggrin	normal to ↓↓↓**	↓↓↓	?[c]

See text. For markers already widely studied, see reference 115. +/↑↓: intensity of presence. We suggest that in the very early forms of extrinsic atopic dermatitis, filaggrin is hardly affected. Abbreviations: APC, antigen-presenting cells; FA, fatty acids; IDEC, inflammatory dendritic epidermal cells; LC, epidermal Langerhans cells; LOX, lipoxygenase; mDC, myeloid dendritic cells; n.d., not determined; pDC, plasmacytoid-derived dendritic cells; PPAR, peroxisome proliferator-activated receptor; TSLP, thymic stromal lymphopoietin.

[a]IDECs are found in the epidermis and dermis, although those present in patients with psoriasis are characterized by different markers and functionality than those present in atopic dermatitis.[117]

[b]Should be determined in humans and dogs with atopic dermatitis.

[c]There is still no genetic pattern associated with filaggrin alterations.

We therefore have a link between the enzymatic disruptions described and the immunoinflammatory disorders in the intestinal barrier and the epidermal barrier (Figure 1).[1] In the intestinal barrier (which is more amenable to study than the skin with its high cellular complexity), 95% of macrophages express the above enzyme (CD11b 12/15 LOX$^+$ macrophages) and the remaining 5% do not (CD11b 12/15 LOX$^-$ macrophages). The predominant CD11b 12/15 LOX$^-$ macrophages produce the anti-inflammatory cytokine IL-10, thereby maintaining a state of immuno/ inflammatory tolerance in as far as the CD11b 12/15 LOX$^-$ macrophages are overall proinflammatory dendritic cells. In 12/15 LOX$^-$ knockout mice, we have previously reported that severe disruption of the filaggrin occurs, accompanied by severe disorders of lipid metabolism due to lack of PPAR activation.[1] In addition, these animals show profound disorders in the trafficking and differentiation of peritoneal macrophages, which behave as proinflammatory cells, both in basal conditions and after exposure to *Staphylococcus epidermidis*.[119] Thus, these macrophages generate more IL-1, IL-3, IL-17, and TGF-β1 and less IL-12 and migratory chemokines. In summary, mutations in the *12/15 LOX* gene or functional deficiencies of the enzyme due to lack of appropriate substrates (fatty acids)[1] could be responsible for the phenomena taking place in intrinsic forms of atopic dermatitis. Moreover, we cannot rule out the participation of these mutations and defects in extrinsic forms of atopic dermatitis, as it has recently been observed that blockade of an IL-3-dependent lectin (Ym1/2), which is abundantly expressed in allergic conditions, leads to decreased production of IL-5 (responsible for eosinophilia in all forms of atopic dermatitis) and IL-13.[120] In addition, production of Ym1/2 in response to IL-13 promotes the production of Th2 cytokines and allergic inflammation through inhibition of 12S-hydroxy-eicosatetraenoic acid by 12/15 LOX.[120] This would explain why systemic or topical supply of some fatty acids might be effective in the treatment of these forms of intrinsic atopic dermatitis (Figure 3). In fact, both our own data obtained through systemic and topical administration of an extemporaneous preparation of olive oil in humans and dogs,[1,40,41] and through topical use of other lipid forms reported by other authors,[121-123] would further support this hypothesis. In addition, this sequence of events would provide a rationale[1] for the causes of disruption of the epidermal barrier in absence of *filaggrin* mutations,[121,123] as well as the weakened defenses of patients with atopic dermatitis against infections caused by *Staphylococcus aureus*.[124]

Returning to the topic of immune complexity (shown in Figure 2 and Table 2) and the new therapeutic lines of

Table 3 Comparison Between Established Treatments and Novel Therapeutic Approaches in Atopic Dermatitis and Psoriasis

	Effects on		Other Effects		
Products	**Composition of EB**	**Immune Mechanisms**	**Antimicrobial**	**HDL-c**	**Secondary**
Classic					
Corticosteroids	No	Yes (suppressant)	No	No	Yes
TCIs	No	Yes (suppressant)	No	No	Yes
Novel					
Ceramides	Yes	No	?	No	No
EPOO	Yes	Yes (regulator)[a]	Yes[b]	Yes[a]	No

Abbreviatons: TCI, EB, epidermal barrier; EPOO, extemporaneous preparation of extra virgin olive oil; HDL-c, high-density lipoprotein cholesterol; TCI, topical calcineurin inhibitors.

[a]By oral route.

[b]In vitro topical form. The effects of corticosteroids are well known and those of ceramides and TCI can be consulted in references 145-147. See text for effects of EPOO. The clinical effects of EPOO should be tested in more controlled clinical trials.

investigation, it should be noted that although IL-10 in its capacity as a pro-Th2 cytokine had been supposed to have a negative impact on the pathogenic mechanisms of atopic dermatitis, there are now sufficient examples to demonstrate its crucial anti-inflammatory role in atopic dermatitis. First, IL-10-producing Treg cells suppress Th2 response to allergens[125] and those induced by TSLP on myeloid and monocyte-derived dendritic cells that, as we saw,[1] are characterized by a proinflammatory Th2 phenotype with high TNF-α production and low IL-10 production in models of asthma and atopic dermatitis.[126] In fact, dendritic cells activated by TSLP induce the production of IL-4, IL-5, IL-13, and TNF-α in Th0 cells, but not the production of IFN-γ or IL-10,[127,128] with the response of Langerhans cells being similar to that of the circulating dendritic cells.[128,129] Second, these same effects are observed during experimental treatment with immunomodulators such as imadazoquinoline[130] and Calmette-Guérin bacillus,[131] in which the suppression of Th2 inflammatory response by IL-10 is also accompanied by elevated production of IFN-γ. (Remember that IL-10 has traditionally been thought to suppress Th1 response and, therefore, IFN-γ production, in addition to other immunodepressor effects.[132]) Third, in a model of Fc receptor depletion, the absence or attenuation of symptoms of atopic dermatitis correlates with increases in IL-10 and Treg cells (FOXp3) in the skin of animals.[133] Fourth, in the above canine model of atopic dermatitis,[91] clinical improvement with allergen-specific immunotherapy was associated with increased serum levels of IL-10 and higher proportions of circulating Treg cells.[93] Fifth, in a pilot study in humans, the partial clinical success of allergen-specific subcutaneous immunotherapy was associated with increased IL-10 levels and decreased specific IgE levels.[134] Sixth, the use of cystatin (a protease inhibitor occurring naturally in humans) inhibits inflammatory and allergic response in an experimental model through production of IL-10, thereby explaining the lower incidence of allergies in subjects with worm parasites.[135] Seventh, transfer of the IL-10 gene suppresses eosinophilia and hyperreactivity to airborne allergens in a murine model through suppression of APC function, without affecting systemic immune response.[136] Finally, the decrease in levels of IFN-γ in peripheral blood is associated with greater risk of atopic dermatitis in the first 2 years of life[137] and more extensive *S aureus* colonization in children with atopic dermatitis.[138]

Everything seems to indicate, therefore, that both IL-10 and IFN-γ are special targets for treatment in atopic dermatitis (Figure 3) and possibly psoriasis. This rationale, along with the PPAR defects described earlier, was used by our group in a study of an extemporaneous preparation of olive oil in patients with atopic dermatitis or psoriasis.[1,40,41] In fact, as reported in this journal for the first time, the extemporaneous preparation of olive oil behaved like a potent inducer of IL-10 and IFN-γ (Figure 4A and B) in a highly inflammatory human model, with high risk of cardiovascular disease and infections, with frequent skin disorders (xerosis, pruritus, and infections) and with severe PPAR signaling disorders,[139] as is the case of patients with chronic renal disease.[36,140] In line with the studies that make a case for so-called outside-to-inside treatments in atopic dermatitis,[121,122] we suggest that oral administration of an extemporaneous preparation of olive oil (an inside-to-outside treatment) would be able to normalize the systemic inflammatory disorders present in atopic dermatitis through the production of IL-10 and IFN-γ by Treg cells (Figure 3), while topical application could provide adequate lipid supply to the epidermal barrier, as well as inducing a local immunoregulatory process (Table 3). On the other hand, the potent antimicrobial activity exhibited in vitro by extemporaneous preparations of olive oil against *S aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger* is a further argument in favor of their use in both diseases (Table 3).[124]

It is important to highlight that although most IL-10 inducers are not usually associated with side effects, particular care is needed when targeting this cytokine. Thus, although recombinant IL-10 showed promising clinical effects in the treatment of psoriasis,[141,142] long-term studies by the same authors have shown the presence of clear undesirable effects.[143,144] In the same pharmacological-toxicological sense, it is important to note the possible side effects arising from chronic use of topical calcineurin

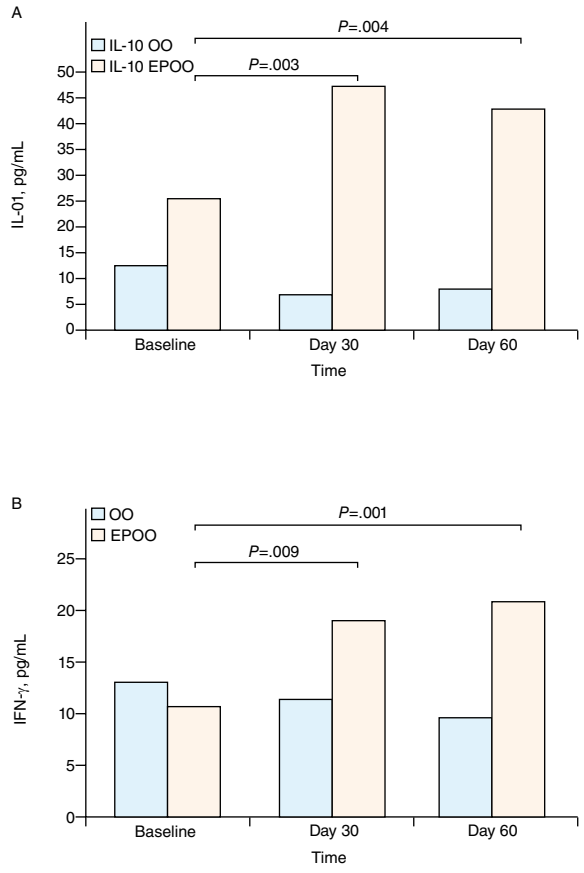

Figure 4 A) Administration of an extemporaneous preparation of olive oil (EPOO) increases serum levels of interleukin 10 (IL-10) and interferon g (IFN-g) in patients with chronic renal disease. Conventional olive oil. Patients took olive oil (OO) or the extemporaneous preparation of olive oil (EPOO) for 30 days. A follow-up period without EPOO of 30 days (day 60) was established, although patients continued to take their usual olive oil. B) Functional classification of atopic dermatitis. FABP indicates fatty acid-binding proteins; IFN-g, interferon g; LC, Langerhans cells; LOX, lipoxygenases; PPAR, peroxisome proliferator-activated receptors; Th, T helper cells.

inhibitors.[145-147] These might be mitigated by taking extemporaneous preparations of olive oil or other lipid-based compounds,[121,122,145] which have been clearly shown not to have any undesirable effects (Table 3).

Given the traditional forms of atopic dermatitis (intrinsic and extrinsic) progress to filaggrin disorders, and taking into account the low prevalence of intrinsic atopic dermatitis (15%-20% of the cases), similar to that arising from functional deficiencies in the gene controlling filigrin,[2,3] the next question is how immune response affects these filaggrin disorders. We believe that intrinsic atopic dermatitis would be the form in which the primary defects of the epidermal barrier play a fundamental initiator role given that extrinsic atopic dermatitis is caused by immune disorders, allergic sensitization, and production of IgE, with a subsequent impact on epidermal barrier disruption.

In fact studies have already been published that implicate IL-4 in suppressing IFN-γ-induced ceramide synthesis[115,148] and recent results reinforce these findings, suggesting that the Th2 responses can inhibit filaggrin expression through upregulation of membrane-associated protein (MAP) 17 by IL-4, IL-6, or IL-22 in keratinocytes (Figure 3).[149] MAP17 is a nonglycosylated protein that amplifies the malignant characteristics of cancerous tumor cells by increasing levels of reactive oxygen species though its molecular domain that fixes PDZ.[150] Interestingly, the *PDZK1* gene is located in the same region of chromosome 1q21 that has been associated with atopic dermatitis and that regulates expression of envelope proteins such as filaggrin, loricrin, and involucrin.[149] Thus, it has been shown that Th2 responses can lead to decreased filaggrin expression through increased expression of MAP17 in keratinocytes (Figure 3). Another interesting point is that overexpression of MAP17 arises because of deficient *PDZK1* genes, leading in turn to deficient hepatic expression of the high-density lipoprotein (HDL) receptor (SR-BI), with the resulting expression of a proatherogenic phenotype (Figure 3).[151] This is particularly important for the purposes of the present article as oral treatment with extemporaneous preparations of olive oil normalizes HDL levels (Table 3) in patients at high risk of inflammation and cardiovascular disease;[36,37] and, as mentioned already,[1] it seems that cutaneous allergic sensitization is inversely related to serum levels of HDL cholesterol.[152,153] Likewise, adult patients with psoriasis are at a high risk of myocardial infarction associated with decreased plasma HDL cholesterol.[154,155]

Conclusions

Although differing in their causal mechanisms and clinical manifestations, atopic dermatitis and psoriasis have pathogenic mechanisms in common. Among these, of note are lipid disruption in the epidermal barrier, deficient expression of PPAR-α receptors and deficient endogenous production of IL-10 and IFN-γ. Certain fatty acids could be used in these situations for therapeutic interventions. These agents, by acting on the substrates of FABP and LOX enzymes, affect the way these enzymes regulate the expression and activation of PPAR. The result is an effect on certain regulatory arms of the immune system (Treg cells). A diet with sufficient fatty acids (or their topical application) would represent important progress in the control of inflammatory bowel and skin diseases. After all, our skin reflects what we eat.

Conflict of Interest

Vicente G Villarrubia is managing director of the Bioaveda SL, a research and development company that holds the rights to the extemporaneous preparation of olive oil mentioned in this article. Dr S Vidal-Asensi, Dr V Pérez-Bañasco, Dr J Cuevas-Santos, and Dr R Cisterna-Cáncer are partners in the same company. This article has been partly funded by the Agencia Invercaria de Capital/Riesgo, of the Andalusian Department of Innovation, Science and Business

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