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Dimethylfumarate for psoriasis: more than a dietary curiosity☆

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Fumaric acid esters (FAEs) have been used for the oral treatment of psoriasis since 1959 and have been registered for this indication in Germany since 1994. Dimethylfumarate (DMF) and its metabolite methylhydrogenfumarate (MHF) are the pharmacologically active compounds, with DMF being the main component of the marketed FAE-mixture. However, the mechanism of action of FAE is yet to be fully understood. It has been shown that DMF inhibits NFκB translocation, which leads to (i) the inhibition of pro-inflammatory cytokine production and adhesion molecule expression, (ii) the inhibition of dendritic cell differentiation and, at higher concentrations, (iii) the induction of apoptosis. Recent evidence also shows that these effects are mediated through the interference of the intracellular redox system by DMF. Here, the mode of action of FAE and its clinical use for psoriasis will be discussed.

Introduction

Fumaric acid is a simple-structured dicarbonic acid, which has an important role in the citric acid cycle in humans (Figure 1). Fumaric acid deficiencies, or other disorders related to a disturbed metabolism of this compound, are unknown as a cause of disease. Nevertheless, fumaric acid esters are the number one drug for the oral treatment of severe psoriasis in Germany.

Fumaric acid is used as a nutritional additive in various forms in the food and farming industries, without untoward effects [1]. The clinical use of fumaric acid derivatives started in 1959 when the German chemist Schweckendiek, suffering from psoriasis, raised the hypothesis that the disease might be caused, at least in part, by disturbances in the citric acid cycle. He postulated that the exogenous supplementation of fumaric acid might reverse the pathological process. Schweckendiek tried to prove his hypothesis by treating himself with fumaric acid derivatives. Because of a potential irritant effect of free fumaric acid when taken orally, he used esters of fumaric acid. Gastrointestinal (GI) irritant effects, however, could not fully be circumvented. Taking a self-designed mixture of different fumaric acid esters (FAEs; see Glossary), his psoriasis cleared [2].

To improve the pharmaceutical quality, a new product consisting of a defined mixture of FAEs, produced by the Swiss company Fumapharm (www.fumapharm.ch), became available [3]. Coating of the tablets enabled the liberation of FAEs in the small intestine and decreased the rate of adverse GI effects. A schedule of dosing was established on an empirical base, starting with the low-strength formulation for three weeks before the introduction of high-strength tablets by increasing the number of tablets weekly. The maximum dose was defined as a total amount of 1.2 g FAE/day (two high-strength tablets three times a day), representing 720 mg dimethylfumarate (DMF). In 1994, this mixture of FAE was registered by the German drug administration (BfArM) as Fumaderm® initial (low-strength tablets) and Fumaderm® (high-strength tablets) for the systemic treatment of severe psoriasis.

Since its official registration, Fumaderm® has become the number one drug for the systemic therapy of psoriasis in Germany (approximately 66% of all prescriptions for systemic psoriasis therapy; 'EUROPSO patient survey

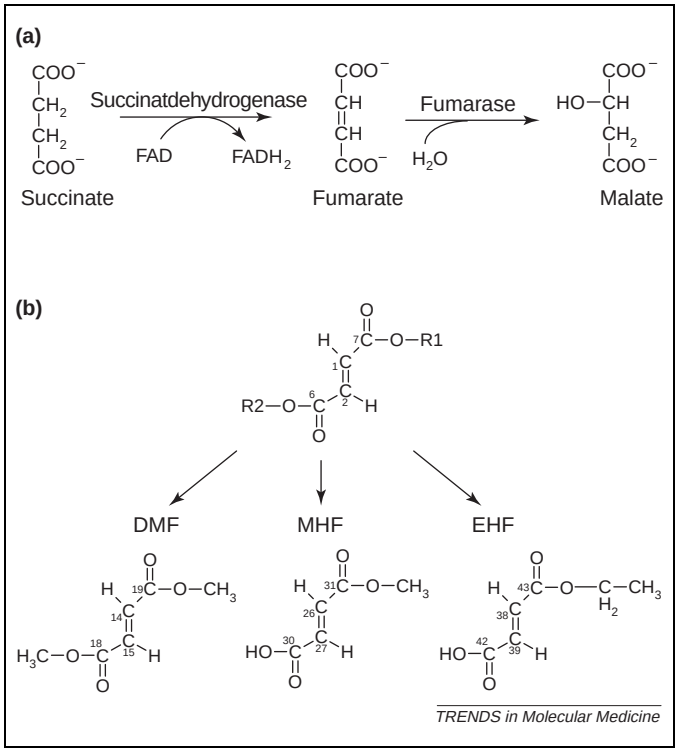

Figure 1. Fumarate and its esters. **(a)** Fumarate metabolism in the citric acid cycle. **(b)** The chemical structure of free fumaric acid ($R_1=R_2=H$) and the fumaric acid esters ($R_1=R_2=$Alkyl) dimethylfumarate (DMF), methylhydrogenfumarate (MHF)

☆Schering AG has no commercial interest in Fumaderm®.

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Glossary

DMF: dimethylfumarate
EHF: ethylhydrogenfumarate
FAEs: fumaric acid esters
MHF: methylhydrogenfumarate
NFκB: nuclear factor κB

2002', www.europso.org). Clinical studies are limited in number; however, the reported efficacy in psoriasis is high, together with a favourable long-term safety profile (see below). The first data concerning combination treatment with FAEs were recently published which broadens the clinical usage in patients with severe psoriasis [4,5].

Within the last few years, there has been increasing evidence that FAEs have potent immunomodulatory effects on various types of cells with importance not only for the psoriatic tissue reaction.

Pathogenetic concepts of psoriasis

Psoriasis is regarded as an immune disorder in which a putative antigen presented to T cells by antigen-presenting dendritic cells leads to the generation of specifically activated T cells [6]. According to the T-cell cytokine expression profile, psoriasis is classified as a Th1-type immune response.

Because several other inflammatory diseases, such as rheumatoid arthritis, Crohn's disease and multiple sclerosis, follow similar immunological pathways of T-cell activation, psoriasis can be regarded as a visible disease model. The crucial involvement of T-cells in the pathogenesis of psoriasis was highlighted by transplantation experiments of psoriasis skin onto severe combined immunodeficiency mice and investigations to analyse the T-cell receptor repertoire [7,8]. In addition to the inflammatory component, the hyperproliferation of epidermal keratinocytes, together with a disturbed cellular differentiation (leading to the disease characteristic hyperparakeratosis), seems to be dependent on a genetic susceptibility that is, among others, associated with the epidermal differentiation complex (psoriasis susceptibility locus; PSORS4) and corneodesmosin (PSORS1) [9].

The mechanism of action of FAEs in psoriasis might, therefore, be of interest for future use in the treatment of diseases with a pathogenetic background similar to this chronic skin disorder. Here, a summary of the current knowledge about the clinical use of FAEs and its mode of action is given.

Clinical use of FAE for the systemic treatment of psoriasis

The consensus guidelines [3] recommend treating psoriasis patients with Fumaderm® until there is an improvement of lesions or the patient is satisfied with the treatment outcome. A maintenance treatment to stabilize clinical improvement can be performed for up to two years. Clinical trials have shown a decrease of the psoriasis area and severity index (PASI) – a measure for psoriasis severity – between 50 and 80% after 12–16 weeks of therapy [10,11].

Recently, Hoefnagel and colleagues [12] presented data patients treated continuously for up to 14 years. Notably, no increased risk for infections or malignancies could be found within this study population.

In earlier clinical trials, the question of which of the different esters of fumaric acid is the active compound was addressed. In 1989, Nieboer *et al.* [13] published the results of an extensive study evaluating the clinical effects of different FAEs in various concentrations as monotherapies and in combination in psoriasis patients. The data showed that ethylhydrogenfumarate (EHF) monotherapy was not superior to placebo. However, by using DMF (240 mg/d), a 40% improvement was seen in the DMF-treated group after six weeks of therapy, whereas in the placebo-group, worsening of psoriasis was reported. It was concluded that the main active ingredient of Fumaderm® is DMF.

Adverse events related to FAE treatment

The most common adverse event reported in all clinical trials with FAE is GI complaints. Clinical symptoms include diarrhoea (most common), stomach ache and cramps, increased frequency of stools, nausea and vomiting. GI-complaints are clearly related to the tablet formulation of FAE. With a newly developed microtablet formulation, the rate of GI complaints is decreased to below 6% (unpublished data*).

Flush is another characteristic adverse event related to FAE-treatment. The symptoms are highly variable and are reported mainly as a transient feeling of warmth or heat normally lasting for minutes. Remarkably, these side effects frequently occur only during the initial phase of therapy. Other symptoms occurring as adverse events during FAE therapy are rare. There is no report about an increased frequency of infections, neither of bacterial (e.g. folliculitis) nor viral origin (e.g. herpes simplex, zoster or human papillomavirus-related infections, such as common warts, common cold or flu). There are no reports in the literature about the development of any form of malignancies (e.g. lymphoma, myeloproliferative disorders and solid tumours) during long-term treatment with FAE.

FAE-induced leukocytopenia is frequently observed [10,14]. Severe lymphocytopenia might be a reason to terminate FAE-therapy. Although there are no published follow-up data in lymphopenic patients after FAE-withdrawal, there is a complete recovery up to baseline values within 6–12 weeks after termination of FAE-therapy (U. Mrowietz, unpublished data).

A characteristic of FAE treatment is an increase in peripheral blood eosinophils [10,11]. Maximum eosinophil numbers are usually seen between week four and eight of therapy with a peak at week six. In individual patients, the percentage of eosinophils in the differential count can exceed 25%. However, clinical symptoms or disorders related to eosinophilia have not been observed. When FAE-therapy is continued, eosinophil numbers normally decline and, in most patients, return to baseline levels [11].

* Langner, A. *et al.* (2004) Results of a phase II study of a novel oral fumarate, BG-12, in the treatment of severe psoriasis. *J. Eur. Acad. Dermatol. Venerol.* 18, 798.

Pharmacokinetics of fumaric esters in humans

There is little knowledge about the pharmacokinetics of FAEs in humans. FAEs are almost completely absorbed in the small intestine. The postulated main active ingredient of Fumaderm®, DMF, is rapidly hydrolysed by ubiquitous esterases to methylhydrogenfumarate (MHF), its main metabolite. MHF is further metabolized into fumaric acid and finally into carbon dioxide and water. There is no evidence for an organ-specific toxicity due to drug metabolism.

Metabolism is independent of cytochrome P-450-dependent pathways. This is of particular importance because psoriasis is frequently associated with other diseases, such as diabetes mellitus or coronary heart disease, requiring concomitant medications [15]. Drug interactions have not been reported.

In a recent investigation in healthy subjects given one tablet containing 240 mg DMF and 95 mg calcium-monoethylfumarate, only MHF, the metabolite of DMF, could be detected in serum after a mean time of 120 min, when the tablet was taken under fasting conditions. DMF and free fumaric acid were below detection limit of the HPLC-system used [16].

By using an intestinal tissue homogenate the half-life of DMF was less than 2 min. The enzymes responsible for DMF degradation are carboxylesterases rather than cholinesterases [17], but the significance of this finding is not yet clear.

Mode of action

FAEs can modulate the functions, including proliferation and mediator production and secretion, of several cell types. Can the various known effects of FAE be linked to a common mechanism of action?

FAEs affect T-cell numbers

Early studies clearly demonstrated that FAEs have profound effects on the T-cell system. In an open study using Fumaderm® in 16 patients with severe psoriasis (PASI > 20), flow-cytometric determination of leukocytes was performed weekly for 12 weeks [18]. Leukocytopenia was observed in 94% of the patients, with a mean reduction in leukocyte numbers of 26.6% (maximum 60%). The number of $CD4^+$ T cells decreased by 45.4% and $CD8^+$ T cells by 44.5%. In one patient, $CD8^+$ cells decreased by 87%; however, clinical signs of immunosuppression-like infections were not observed.

In seven of 16 patients, absolute numbers of $CD4^+$ T cells were ~200/μl. There was no change in the CD4:CD8 ratio. HLA-DR-expression on T cells remained unaltered and there was no significant alteration in CD25 expression (IL-2 receptor α-chain). The decrease in the number of peripheral T cells is associated with a reduction of the lesional T-cell infiltrate. An immunohistochemical study of 33 patients, from whom biopsies were taken before and after two, six and eight weeks of Fumaderm® therapy, revealed a decrease in the epidermal inflammatory infiltrate of 74.4% after eight weeks of treatment, with a decrease of $CD4^+$ T cells of 51.2% [19]. The subepidermal infiltrate decreased by 52.1%, with a reduction in $CD4^+$ cells of 84.4% after eight weeks. within the epidermis from 26.8% to 33%, in the subepidermal layer from 28.9% to 33.6% and decreased in the deeper dermis from 20.3% to 11.9% after eight weeks of Fumaderm® therapy. Within the eight-week treatment period there was a complete clearing of neutrophil granulocytes from the skin in pre-treatment biopsies. Although treatment with fumarates lead to a profound decrease in the number of T cells in some patients, which might be a reason to stop therapy, adverse events related to a decreased immunosurveillance have not been observed in short term or long-term studies [12].

In an *in vitro* study, the effect of MHF on T-cell cytokine production was analysed in greater detail [20]. The authors demonstrated, in purified T cells (98% $CD2^+$) stimulated with antibodies against CD2, CD28 or a mixture of CD28 and CD3, that <200 μM MHF did not influence cell proliferation. MHF induced the production of the Th2-type cytokines IL-4 and IL-5 (EC_{50} 100 μM), but was without effect on IL-2 or IFNγ production, which are prominent Th1-type cytokines. The stimulating effect of MHF on IL-4 and IL-5 production was also shown for several different T-cell clones. By using radioactively labelled MHF and DMF, evidence for specific binding sites for MHF on T-cells was provided. In a separate set of experiments, $CD4^+CD45RO^+$ memory T cells were stimulated with antibodies against CD2 and CD28 and the effect of MHF was evaluated. MHF upregulated the secretion of IL-4 2.5-fold and IL-5 threefold in stimulated memory T cells, without any effect on IFNγ secretion. The induction of IL-4 and IL-5, but not of IFNγ, by MHF was further seen in peripheral blood mononuclear cells (PBMCs) stimulated with purified protein derivative (PPD) as a pathogenic stimulus, mimicking an immune response against *Mycobacterium tuberculosis*. MHF enhanced the release of TNFα and IL-10 in lipopolysaccharide-stimulated monocytes without having an effect on IL-12 and IL-1RA secretion [21]. Newer data showed a reduced secretion of IFNγ after the treatment of dendritic cells with MHF and subsequent T-cell stimulation [22].

Goreschi *et al.* (unpublished data†) analysed the *ex vivo* Th1- and Th2-cytokine repertoire of T cells from patients with psoriasis treated with FAEs. They found a significant suppression of the intracellular IFNγ:IL-4 ratio in $CD4^+$ T cells, which began after three weeks of therapy and paralleled clinical improvement.

From these data, it was concluded that the main mechanism by which FAE induces the remission of psoriatic lesions is a shift of the immunological balance from a Th1- towards a Th2-like response. However, the prominent decrease in the number of T cells that is associated with FAE therapy prompted the investigation of the effect of these compounds on programmed cell death.

FAE-induced apoptosis

In U937-cells, Seböck *et al.* [23] were the first to demonstrate the potent apoptosis-inducing activity of

† Goreschi, K. *et al.* (2002) Fumaric acid ester an anti-psoriatic drug abolishes the capacity of T cells to induce Th1-mediated autoimmune disease. *Arch. Dermatol. Res.* 294, 28. Presented at the XXIX Annual meeting of the Arbeitgemeinschaft

DMF. These data were confirmed in human monocyte-derived dendritic cells as an important regulator of specific T-cell activation. Zhu and Mrowietz [24] showed that DMF and MHF could completely prevent the GM-CSF- and IL-4-induced differentiation of monocytes into dendritic cells. DMF also potently induced apoptosis in these cells.

Recently, the effect of FAEs on T-cell apoptosis was investigated in greater detail. In purified human T cells, DMF, but not MHF, could induce apoptosis. This was substantiated by measuring two independent markers [Apo2.7 expression and DNA fragmentation, using TUNEL (Tdt-mediated dUTP nick end labeling)]. T cells stimulated with IL-2, antibodies against OKT3 or both were more susceptible to DMF-mediated apoptosis compared with unstimulated cells. In parallel to an increase in *Apo2.7* expression, DMF induced a dose-dependent down-regulation of anti-apoptotic *Bcl2*-expression [25].

FAEs modulate cytokine production

In a series of experiments, the effect of FAEs, notably DMF, on inflammatory mediator transcription and production was investigated. Using human PBMCs, DMF inhibited lipopolysaccharide-induced protein secretion of the chemokines IL-8, Mig and IP-10 in a dose-dependent manner without altering cell viability [27].

Because keratinocytes themselves are actively producing inflammatory mediators, such as chemokines, Stoof *et al.* [26] investigated the effect of DMF on phorbol-ester- or IFNγ-stimulated normal human keratinocytes obtained from healthy human skin. They showed that DMF caused a dose-dependent inhibition of groα, IL-8, Mig, IP-10 and IP-9/I-TAC mRNA expression. Furthermore, protein secretion of IL-8, Mig and IP-10 was decreased by the DMF treatment of keratinocytes.

Ockenfels *et al.* [27] co-cultured normal human keratinocytes obtained from patients with psoriasis together with HUT78-cells (a T-cell-like cell line). DMF inhibited IFNγ, IL-6 and TGFα release and increased IL-10 release in all co-culture experiments.

FAE modulates adhesion molecule expression

Because the inflammatory response in psoriasis is associated with an increased expression of adhesion molecules on endothelial cells and keratinocytes [28], the effect of FAEs was investigated. Vandermeeren and co-workers [29] showed that DMF inhibited TNFα- or IL-1α-stimulated expression of the adhesion molecule ICAM-1 in human fibroblasts.

In human umbilical vein endothelial cells (HUVECs), DMF blocked the TNFα-induced expression of the adhesion molecules ICAM-1, VCAM-1 and E-selectin [29]. Furthermore, the adherence of monocytic U937 cells to TNFα- and IL-4-treated HUVECs was inhibited by DMF.

FAEs inhibit NFκB activity

Because the transcription of chemokines and adhesion factors, including IL-8 and E-selectin, is dependent upon NFκB, it is possible that DMF modulates this regulatory pathway. Additional evidence for a possible role of NFκB in part, dependent on the modulation of NFκB activity as a regulator of cell survival. Bureau *et al.* [30] demonstrated the importance of constitutively active NFκB for the survival of quiescent mature immune cells, such as T and B cells, monocytes and macrophages and neutrophil granulocytes. The blockade of NFκB lead to apoptotic cell death in human macrophages, which depended on the activation of caspase 9, but not caspases 3 or 8 [31]. In human T cells, the inhibition of NFκB translocation was associated with apoptotic cell death independent of caspases 1 and 3 [32]. Ward *et al.* [33] found TNFα to be a survival factor for neutrophils linked to NFκB activation.

When the effect of DMF on the NFκB-pathway was analysed more closely, a significant inhibition of κB1/p50 in the nucleus was found, whereas there was little influence on IκBα, β and ε or RelA/p65 or c-Rel. AP-1-mediated gene transcription remained unaltered [34].

The effect of DMF on the NFκB cascade was further investigated using the TNFα- or VEGF-induced mRNA expression of tissue factor in human endothelial cells [35]. DMF inhibited TNFα-, but not VEGF-, induced tissue factor expression. Further experiments revealed an inhibition of TNFα-mediated nuclear entry of p65. This was not due to the inhibition of TNFα-induced signalling to IκB, because IκBα phosphorylation and degradation were not altered [36]. By interfering with NFκB translocation, DMF acts not only as an inhibitor of TNFα-induced cellular functions but also as an inhibitor of TNFα-production, because its transcription is, at least in part, dependent on NFκB.

Litjens *et al.* [22] provided evidence that, in addition to DMF, MHF inhibited LPS-induced NFκB activation in human dendritic cells.

FAEs interfere with cellular redox-systems

Barchowsky *et al.* [37], using porcine aortic endothelial cells, found an association between DMF-mediated inhibition of NFκB translocation and intracellular thiol levels. The phosphorylation and ubiquitination of IκB is dependent on the balance of reduced glutathione (GSH) and oxidized glutathione-disulfide (GSSG), which is influenced by intracellular reactive oxygen species (ROS) through redox-sensitive kinases [38].

Data from the toxicology literature indicate a direct link between cell death by necrosis or apoptosis and intracellular levels of thiols. In a model of acetaminophen-induced liver toxicity, hepatocyte necrosis was observed in relation to decreased glutathione levels [39]. The addition of antioxidant glutathione-monoethylester shifted necrotic cell death to apoptosis. An increase of oxidized and a reduction of reduced glutathione lead to increased apoptosis in M14 melanoma cells, which was associated with a downregulation of the c-myc protooncogene [40].

The effect of DMF on intracellular thiols is time dependent. The addition of DMF to Chinese hamster ovary cells for 5 min was followed by a decrease of intracellular glutathione to 10% of basal levels [41]. When the activity of the glutathione-synthesis-limiting enzyme γ-glutamine–cysteine synthase in guinea pig hippocampus cells was inhibited by the addition of the

levels of reduced glutathione were decreased by 30% [42]. The subsequent addition of DMF further reduced glutathione to 4% of baseline levels. However, Duffy *et al.* [43] demonstrated an increase of glutathione in a retinal-neuroblastoma hybrid cell-line by DMF. This discrepancy was further investigated by using human retinal pigment epithelial cells. Nelson and co-workers [44] found a time-dependent effect of DMF on intracellular thiols: an initial decrease of glutathione followed by a sustained increase of more than twofold.

These data were confirmed in animal experiments in which DMF was added to the diet of mice and rats for two weeks, leading to a significant increase of glutathione and quinone-reductase, which is another detoxifying enzyme that is found in various organs, such as the liver and small intestine [45].

From these experiments, it can be concluded that DMF can significantly modulate intracellular levels of detoxifying enzyme systems, such as the GSH–GSSG system, upregulating reduced-glutathione levels after prolonged exposure or dietary supplementation. There are no data about the activity of MHF in these systems.

FAEs: hypothesized molecular mode of action

Taken together, the following hypothesis about the mechanism of action of DMF can be proposed: (i) DMF interferes with intracellular thiols resulting in increased levels of reduced glutathione after prolonged exposure, through an unknown mechanism; (ii) increased glutathione levels inhibit redox-sensitive kinases, resulting in (iii) an inhibition of the phosphorylation and ubiquitination of IκB, leading to (iv) an inhibition of NFκB translocation (Figure 2). This pathway leads to the modulation of the NFκB-dependent cascades of inflammatory cytokine production and adhesion molecule expression. Because DMF seems not to interfere with the basal cytokine expression that is necessary for immune defence reactions, the documented long-term safety regarding the lack of an increased risk of infections or tumour development might be explained.

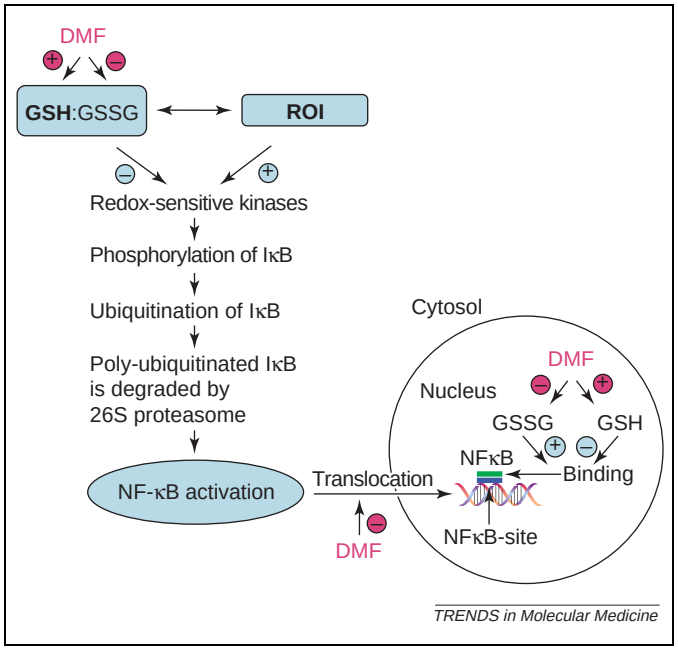

Figure 2. Proposed mode of action of DMF on NFκB-regulated gene transcription. The balance between oxidized glutathione (GSSG) and reduced glutathione (GSH) as well as the presence of reactive oxygen intermediates (ROI) regulates degradation of the inhibitor of κB (IκB) and subsequent activation of NFκB. DMF increases GSH, leading to an inhibition of NFκB-activation. Furthermore, DMF inhibits NFκB p65 subunit translocation from the cytosol into the nucleus, and by increasing GSH levels decreases the binding of NFκB to DNA.

Concluding remarks

The empirically observed effect of FAE on the immunologically mediated skin disease psoriasis has led to the discovery of the potent immunomodulatory activity of the active compound DMF. FAEs, particularly DMF, might be regarded as potent immunomodulators with clinically proven effectiveness in psoriasis. From the present data, the inhibition of NFκB translocation and downstream NFκB-dependent pro-inflammatory pathways are the hallmarks of the mode of action of DMF. The interference with intracellular redox-systems might lead directly to the effects observed.

Unfortunately, the product approved only in Germany (Fumaderm®), being a mixture of different FAEs composed by empirical means, could not be licensed elsewhere. However, a new drug, termed BG-12, is currently in clinical development and consists of DMF as a monosubstance in a microtablet formulation.

Future research should be directed towards determining free fumaric acid, interact with intracellular structures and components at the molecular level. The establishment of more sophisticated methods for analysing FAE metabolism *in vivo* and *ex vivo* is an essential prerequisite. The identification of the mode of action of FAEs in more detail might lead to the identification of promising new drug targets. More clinical studies are also needed; these should include larger patient populations over longer periods of time, to verify the suspected favourable long-term safety.

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