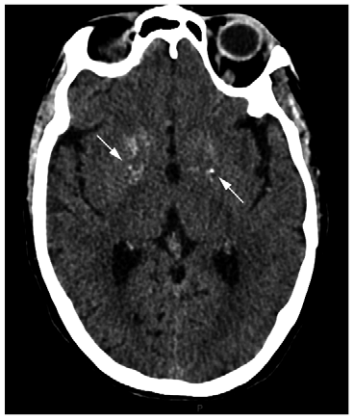

Figure 2 Brain tomodensitometry (without iodinated contrast) showing calcifications (white arrows) of the basal ganglia.

retained.[4] Within 72 h after treatment initiation, the cognitive function was restored, both paresthesia and tetany disappeared, and skin lesions were greatly reduced (Fig. 1b). Electrocardiography findings, calcemia and phosphoremia levels normalized. After 1 year of calcium and vitamin supplementation, the patient remained psoriasis-free and the calcium level was within the normal range.

Pustular psoriasis is an inflammatory variant of psoriasis, characterized by the infiltration of neutrophils in the epidermis leading to the development of sterile pustules. Generalized pustular psoriasis (GPP), also known as von Zumbusch psoriasis, is an acute rare and severe presentation of psoriasis with skin lesions accompanied by general symptoms such as fever and chills.[5] Fahr's syndrome, also known as bilateral striopallidodentate calcinosis, is a rare (and often asymptomatic) neurological disorder defined by the presence of bilateral intracranial calcifications that can be related to hypocalcaemia.[4] To our knowledge, this is the second report of severe hypocalcaemia associated with GPP and Fahr's syndrome.[6]

Generalized pustular psoriasis can occur in genetically predisposed patients (CARD14 and IL36RN variants) and is also induced by sunburn, medications (e.g. salicylates, glucocorticoids, chloroquine and beta-blockers) or hypocalcaemia.[3] The pathogenic link between hypocalcaemia and psoriasis is not entirely understood, but both *in vitro* and *in vivo* studies have shown that calcium is a key regulator of keratinocyte proliferation and differentiation.[7] Topical $1,25(OH)_2D3$ analogs are effective for psoriasis by both genomic and non-genomic mechanisms.[8] Hence, our case underlines the need to screen for hypocalcaemia in patients presenting late-onset psoriasis and/or non-skin disease manifestations to avoid delayed diagnosis and enable for prompt treatment of the underlying cause.

All authors had full access to all of the data in the case. M. Tissier, S. Abou Nakad and M. Groh drafted the manuscript. All authors involved in critical revision of the manuscript.

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Anti-TNF-α therapy modulates mTORC1 signalling in hidradenitis suppurativa

Editor

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent and debilitating skin disease of the hair follicle, which usually occurs after puberty with painful, deep-seated, inflammatory lesions in the apocrine gland-bearing areas of the body, most commonly in axillary, inguinal and anogenital regions.[1] Mechanistic target of rapamycin (mTOR) is a serine/threonine kinase, which acts as the central component of two distinct complexes known as mechanistic target of rapamycin complex (mTORC) 1 and mTORC2.[2] mTOR dysregulation is involved in a number of either inflammatory or neoplastic conditions as well as in metabolic disorders.[3] We have previously showed mTOR involvement in some of the most common inflammatory dermatoses, including HS.[4,5] Recently, biologics are emerging in the

management of HS, and, in particular adalimumab (ADA), an anti-TNF-α, is the only FDA-approved biologic available for the therapy of moderate-to-severe HS. The aim of this study was to analyse the effects of ADA therapy on mTORC1 activity in patients with HS. ADA administration for patients with HS was 160 mg as an initial dose, followed by 80 mg for 2 weeks and finally 40 mg weekly.[6,7] Clinical response after 16 weeks of ADA therapy was assessed through Sartorius score (Ss) as follows: excellent (Ss reduction of at last 20 points or an achievement of physician global assessment, PGA, of clear) in seven patients, medium (Ss reduction of 10–19 points or a 1-grade improvement of PGA relative to baseline) in three patients and low (Ss reduction of less than 10 points or no grade improvement of PGA relative to baseline) in three patients (Fig. 1a). Globally, Ss and dermatology life quality Index (DLQI) were significantly reduced at W16 (***$P < 0.001$) (Fig. 1b). mTOR gene expression was significantly upregulated in HS lesional skin at W0 compared with healthy skin (Fig. 1c). Moreover, we showed, for the first time, that ADA therapy strongly reduced mTOR at W16 (Fig. 1c). Immunofluorescence analysis demonstrated that ADA at W16 modulates mTORC1, acting on one of its effector proteins: ribosomal protein S6 kinase 1 (S6K1) and its activated form P-S6K1. Both proteins were found to be increased in HS lesional skin, and ADA was able to reduce them at W16. Interestingly, the intensity of staining after therapy correlated with clinical response. The greater the clinical response, the more evident the decrease in levels of S6K1 and P-S6K1 (Fig. 2). This difference was stronger regarding the activated form, P-S6K1,

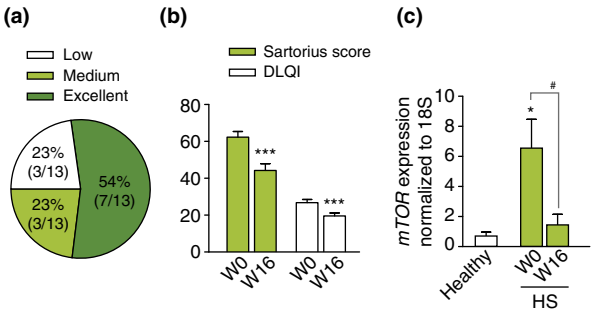

Figure 1 Percentage of clinical response in patients with HS after 16 weeks of adalimumab (ADA) therapy (a). Mean values of Ss and DLQI of study population before (W0) and after 16 weeks of ADA treatment (b). Statistical significance was assessed with paired *t*-test. ***$P < 0.001$; Ss, Sartorius score; DLQI, dermatology life quality index. mTOR gene expression in healthy skin as well as in HS lesional skin at baseline (W0) and after 16 weeks (W16) of ADA therapy (c). Values are normalized to the housekeeping gene 18S and expressed as mean ± standard deviation. Statistical significance was assessed using Mann–Whitney test for the comparison with healthy (*$P < 0.05$) and paired *t*-test ($^{\#}P < 0.05$) for the analysis of ADA treatment (W16 vs. W0).

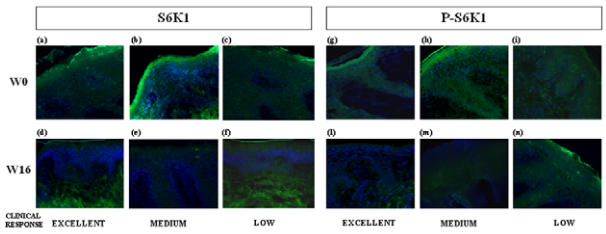

Figure 2 S6K1 (a-f) and P-S6K1(g-n) protein levels in HS lesional skin at baseline (W0) and after 16 weeks (W16) of ADA therapy. Intensity of staining at W16 correlates with clinical response (excellent, medium and low). Magnification 20×.

highlighting the specific involvement of mTORC1 in HS pathogenesis. Our observed mTOR increase in HS lesional skin is in line with our previous evidences[4,5,8,9] and is supported by the fact that TNF-α modulates several targets including mTOR pathway. Indeed, TNF-α suppresses tuberous sclerosis (TSC) 1 resulting in mTORC1 activation. When active, mTORC1 phosphorylates and activates its downstream effector S6K1.[10] Additionally, for the first time, we demonstrated that mTOR gene expression was reduced after 16 weeks of ADA therapy in HS lesional skin, suggesting the tight relationship between mTOR pathway and TNF-α. To deepen understanding, we analysed S6K1 as well as P-S6K1 protein levels by immunofluorescence analysis. A strong staining of both mediators was found in HS lesional skin at W0, and ADA therapy was able to decrease both protein levels at W16 (Fig. 3). A major decrease in S6K1 and P-S6K1 was found in patients with HS, excellent responders to

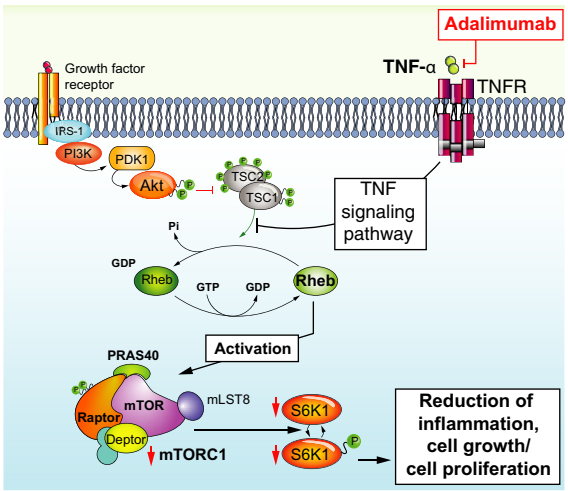

Figure 3 Overview of adalimumab action mechanism that inhibits mTOR pathway.

ADA (Fig. 2). In psoriasis, a strong action on mTORC1 of etanercept, anti-TNF-α agent, has previously assessed. Here too, the difference in staining of P-S6K1 was observed in responder and non-responder patients.[8] In conclusion, mTORC1 pathway is modulated by anti-TNF-α treatment, highlighting a possible new mechanism by which TNF-α inhibition improves HS.

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Titanium dioxide nanoparticles and frontal fibrosing alopecia: cause or consequence?

Dear Editor,

We read with interest the publication by Brunet-Possenti *et al.*[1] who report on the presence of titanium dioxide nanoparticles (TiO_2 NP) along the hair shafts of a patient suffering from frontal fibrosing alopecia (FFA). Given the widespread use of TiO_2 NP in leave-on cosmetics, and particularly in sunscreens, and the recent publications reporting a 'possible' association between the use of sunscreens and the development of FFA[2,3], the authors suggest that a T-cell-mediated allergic response to TiO_2 NP, as occurs to metals involved in some cases of oral lichenoid lesions, might also be important in the pathophysiology of FFA. This would then in turn offer a possible explanation for the rising incidence of this disease.

With respect to this hypothesis and the excellent technical work-up performed by the authors, we take the liberty of formulating some comments that nuance, but also complete their observation. The proposed relationship between the use of sunscreens and the rising (yet still rare overall) incidence of FFA, in both women and men, is not undebated[4–6]. With regard to the detection of TiO_2 NP, the majority of which being rather *micro*particles (>100 nm) than nanoparticles, along the hair shafts in the reported patient, besides being a potential *cause* of FFA, it may also simply be a *consequence* of a more frequent application of TiO_2 NP-containing cosmetics. Furthermore, although the authors clearly confirm that TiO_2 NP may effectively be present along hair shafts, their suggestion that these NP also elicit a T-cell-mediated response remains hypothetical. Indeed, although patch testing titanium salts may represent a challenge[7], no patch tests (nor *in vitro* tests) were performed in this case.

At the Antwerp department, eight females (median age 58.5 years old; range 36-73 years old), all suffering from FFA, were patch-tested with five different, commercially available patch test materials containing titanium: titanium dioxide 10% pet., titanium (III) nitride 5% pet., titanium (IV) oxalate hydrate 5% pet., titanium 10% pet. and calcium titanate 10% pet. (all from Chemotechnique®, Vellinge, Sweden), as well as with TiO_2 NP 25% in cremor cetomacrogolis, an in-house preparation with TiO_2 NP being an ingredient of a commercialized sunscreen, kindly provided to us by the respective cosmetic manufacturer (Mylène®, Heist-op-den-Berg, Belgium); cremor cetomacrogolis was also patch-tested as a control in all eight subjects. Patch test chambers from Allergeaze® (SmartPractice, Calgary, Canada) were used, and following a 2-day occlusion with Fixomull® stretch (BSN medical GmbH, Hamburg, Germany), reactions were read according to the European Society of Contact Dermatitis (ESCD) guidelines[8] on days 2, 4 and 7. No positive reactions could be observed. Although we did not verify the presence of TiO_2 NP along the hair shafts in these eight patients, many of them were found to have regularly applied facial cosmetics (including sunscreens) containing TiO_2 NP. Our observation would thus make a *direct* aetiological role for TiO_2 NP in the development of FFA less likely, yet their potential presence along the hair shafts is still of interest considering the role such NP may play as a so-called cofactor in the development (induction and/or elicitation) of contact-allergic T-cell responses. Indeed, Smulders *et al.*[9] have recently shown that TiO_2 NP modulate (increase) the dermal sensitization potency

