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SHORT COMMUNICATION

Epidermal Insulin Resistance as a Therapeutic Target in Acanthosis Nigricans?

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Acanthosis nigricans (AN) is a condition characterised by hyperpigmented, papillomatous and hyperkeratotic skin that typically presents at intertriginous sites such as the neck or the axilla (1). Although AN is often associated with malignancy, it can also occur with obesity and insulin resistance (2). Here we report improvement of epidermal insulin signalling along with clinical improvement in a patient with AN under treatment with the GLP-1 analog liraglutide.

CASE REPORT

A 42-year-old woman with a BMI of 44.7, a HBA1C of 6.3, and a huge hyperpigmented papillomatous plaque on her abdomen diagnosed as AN (Fig. S1a[1]) was referred to us for optimisation of her type II diabetes mellitus therapy, hitherto treated with metformin, pioglitazone and insulin. The patient was treated with the GLP-1 analogon liraglutide (initially 0.6 mg/day, increased to 1.2 mg/day); metformin was continued, while pioglitazone and insulin were discontinued. Within 3 months, we observed marked clinical improvement of her AN (Fig. S1[1]), paralleled by a drop of the HBA1C to 5.7.

There is increasing evidence that insulin plays a role in skin homeostasis (3, 4) and that epidermal insulin resistance contributes to different skin pathologies (5, 6). We therefore studied the changes in epidermal insulin signalling during anti-diabetic treatment. Insulin resistance is mediated by inhibitory serine phosphorylation of insulin receptor substrate-1 (IRS-1), that blocks signalling from the receptor (7). We found that IRS-1 is strongly phosphorylated in non-lesional (Fig. 1a) and lesional skin (Fig. 1c) at serine 636/9, which decreases during anti-diabetic therapy in non-lesional skin (Fig. 1b), while only a slight reduction can be seen in lesional skin (Fig. 1d). In contrast, the phosphorylation of other serine residues is weak (Fig. 1e–h) or not detectable (Ser307). As serine 636/9 is mainly phosphorylated by the mTOR1 complex (8), we examined the phosphorylation of the mTOR kinase and found strong activation of this kinase in lesional and non-lesional skin (Fig. 1 i, k). mTOR activity decreases during anti-diabetic treatment, but only in non-lesional skin (Fig. 1j). In contrast, total mTOR protein is hardly regulated (data not shown). However, no activation of signalling molecules downstream of mTOR, such as the ribosomal protein S6 or 4E-BP could be detected (data not shown).

Signalling from the insulin receptor via IRS-1 is mediated through the PI-3K/Akt pathway. We found reduced activation of Akt as measured by phosphorylation of serine 473 (Fig. 1m) in non-lesional skin, which increases during anti-diabetic therapy (Fig. 1n), together with an increase in Akt protein (data not shown). Interestingly, we could measure activation of Akt in lesional skin in suprabasal layers, that remains unchanged under therapy (Fig. 1o, p).

DISCUSSION

To date there is only limited data on the pathophysiological mechanisms that link AN to diabetes mellitus. It is assumed that insulin resistance produces compensatory hyperinsulinaemia that results in activation of insulin-like growth factor-1 (IGF-1) receptors which drive the proliferation of keratinocytes and fibroblasts, leading to the observed acanthosis (9). Our data suggest an additional mechanism which may explain how the metabolic condition can lead to dermatological manifestations. We previously demonstrated that insulin regulates the epidermal balance between keratinocyte proliferation and differentiation and thereby contributes to skin homeostasis (6). Here we show that in AN, keratinocytes are unable to respond to insulin properly, as shown through inhibitory IRS-1 phosphorylation, which could interfere with insulin-dependant skin homeostasis. At the same time the growth promoting effects of insulin via the IGF-1 receptor persist (10), which might explain the hyperactivation of Akt in lesional skin. This is underlined by the fact that the anti-diabetic therapy not only ameliorated the skin symptoms of the patient, but also normalised insulin signalling in the epidermis, as measured by a reduction of inhibitory IRS phosphorylation. This effect is especially strong in non-lesional skin, which might imply that in lesional skin the deregulation of insulin signalling prevails despite therapy. Interestingly, we found activation of Akt in lesional skin at all times. We suggest that this pathological activation might be mediated by another signalling pathway such as the IGF-R through hyperinsulinaemia. We have seen similar effects in other hyperproliferative, inflammatory skin pathologies, where keratinocytes despite being resistant to insulin show hyperactivation of Akt through another signalling route, which then mediates pro-proliferative cues (6). Our data suggest that in the AN patient hyperphosphorylation of IRS is mediated via mTOR, which is supported by numerous reports that describe phosphorylation of serine 636/9 by the mTOR pathway (11–13). Nevertheless it cannot be excluded that

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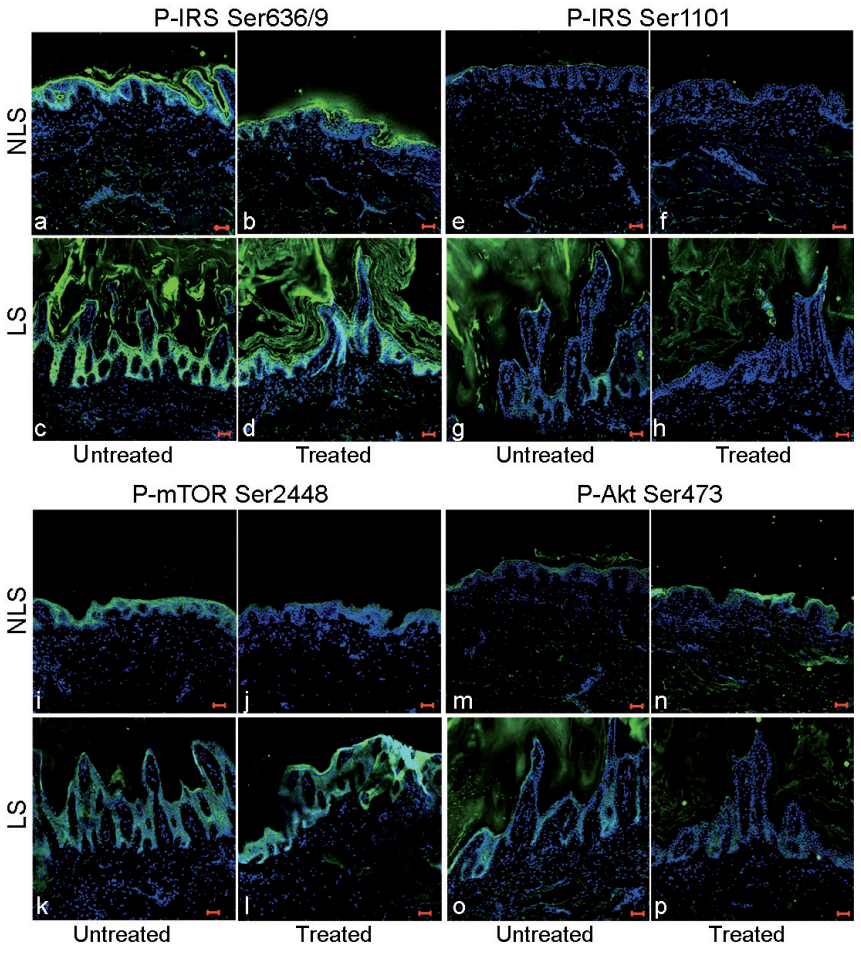

Fig. 1. Punch biopsy cryosections from lesional skin (LS) and non-lesional skin (NLS) of the patient with acanthosis nigricans were obtained before and 3 months into therapy with liraglutide and stained with 2 different phospho-IRS-1 antibodies (a–h) or phospho-mTOR Ser2448 antibody (i–l) or phospho-Akt Ser473 antibody (m–p). Nuclei were stained with DAPI (blue). Overlay images are shown. Bars represent 50 μm.

other kinases such as JNk or Erk1/2 might be responsible for the phosphorylation of IRS-1 at this site. However, mTOR is chronically activated in various tissues under conditions of energy and nutrient overload produced by obesity and contributes to the manifestation of type 2 diabetes (14). In our patient we found a similar regulatory mechanism of mTOR activity. mTOR does not seem to be hyperactivated through over-expression, instead the metabolic imbalance seems to lead to strong epidermal mTOR activation which then causes epidermal insulin resistance. This prevents balancing signals through the insulin receptor/IRS route while the pro-proliferative signals overweigh and in turn contribute to the manifestation of the AN phenotype. Through the optimised anti-diabetic therapy, activation of mTOR is normalised at least in non-lesional skin which releases the epidermal cells from insulin resistance and restores Akt signalling; this is different from the pathological Akt signalling in lesional skin. Thus, our example shows a putative role of mTOR in diabetes-associated AN, which suggests the exploration of the pharmacologically well-established mTOR inhibitor rapamycin/sirolimus as a therapeutic option for AN.

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