

undergoing standard phototherapy. In patients (e.g. psoriasis) with long-term maintenance phototherapy, the determination of serum folate may be advisable.

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DOI: 10.1111/jdv.16419

# PI3K/AKT/mTOR pathway activation in actinic cheilitis and lip squamous cell carcinomas

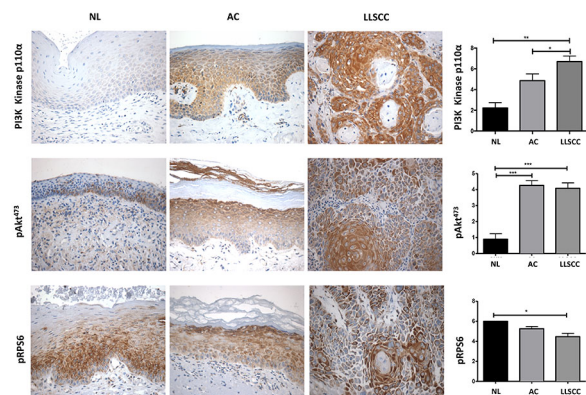
Editor

Lower lip squamous cell carcinoma (LLSCC) is one of the most common cancers of the head and neck.<sup>1</sup> Actinic cheilitis (AC) is a potentially malignant disorder of the lip, and it is estimated that 3.07% of AC cases undergo malignant transformation.<sup>2</sup> Lip carcinogenesis is directly associated with exposure to ultraviolet (UV) radiation and tobacco.<sup>1,2</sup> The molecular circuitry involved in this process, however, remains poorly understood. The identification of deregulated pathways during the process of carcinogenesis may help in the identification of molecular markers capable of identifying early cellular transformation. The activation of the pathway comprised by phosphatidylinositol-3-kinase (PI3K), protein kinase B (Akt) and mammalian target of

rapamycin (mTOR) is considered a key event in many types of tumours due to its ability to modulate important oncogenic outcomes.<sup>3–5</sup> Remarkably, this pathway had never been fully investigated in lip carcinogenesis until now. Herein, an immunohistochemical assessment of PI3K Kinase p110 $\alpha$ , Akt<sup>Ser473</sup> phosphorylation and mTORC1 activation through analysis of ribosomal protein S6 kinase (RPS6) phosphorylation was performed in 38 cases of AC, 40 cases of LLSCC, and nine cases of normal lips (NL), as baseline controls. For each case, an immunoreactive score (IRS) was designated by multiplying the percentage of positive cells (0 – 0% to 10%; 1 – 11% to 50%; and 2 – 51% to 100%) by the staining intensity (0 – absent; 1 – weak; 2 – moderate; 3 – intense). Differences in the IRS were assessed through statistical analysis.

PI3K Kinase p110 $\alpha$  showed a significant increase in immunoreactivity from NL to LLSCC ( $P < 0.01$ ) and from AC to LLSCC ( $P < 0.05$ ) (Fig. 1), suggesting that the activation of this protein is associated with the acquisition of the malignant phenotype. PI3K pathway alterations occur in 30% to 66% of head and neck squamous cell carcinomas and are also linked to advanced disease.<sup>5</sup> The oncogenic triggering of this pathway commonly occurs by activating mutations in the p110 $\alpha$  isoform of PI3K or through the loss of the PTEN tumour suppressor.<sup>5</sup>

The pAkt<sup>Ser473</sup> marker was significantly higher in AC ( $P < 0.001$ ) and in LLSCC ( $P < 0.001$ ), both compared to NL (Fig. 1), suggesting that Akt modification occurs as an early event in lip carcinogenesis. The Akt pathway is considered an important element in cell survival and proliferation after UV exposure,<sup>6</sup> which could justify why AC presents high levels of



**Figure 1** Representative images of immunohistochemical labeling of PI3K Kinase p110 $\alpha$ , pAkt<sup>Ser473</sup>, and pRPS6 in NL, AC and LLSCC (original magnification,  $\times 400$ ). Mean expression of PI3K Kinase p110 $\alpha$ , pAkt<sup>Ser473</sup>, and pRPS6 in NL, AC and LLSCC (\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$  – Kruskal–Wallis test followed by Dunn’s *post hoc* test adjusted for Bonferroni error correction).

pAkt. Moreover, other groups have previously demonstrated an increase of pAkt<sup>Thr303</sup> in oral squamous cell carcinoma (OSCC) and oral epithelial dysplasia compared to non-dysplastic oral tissue,<sup>4</sup> corroborating with the present findings. Several PI3K/Akt/mTOR target drugs are available, and their use as a topical treatment for AC deserves to be further investigated.

The activation of mTORC1 that results in phosphorylation of RPS6 was significantly decreased in LLSCC when compared to NL ( $P < 0.05$ ), contrasting with the previous proteins (Fig. 1). These findings agree with previous studies conducted with OSCC and leukoplakia.<sup>4,7</sup> Moreover, our group has previously studied the PI3K/PTEN/mTOR pathway in lip keratoacanthoma (KA),<sup>8</sup> a well-differentiated, well-keratinized tumour that may originate in the pilosebaceous unit. We observed a strong positivity for pRPS6 along with a lower expression of pAkt<sup>Ser473</sup>. Our hypothesis is that mTORC1, but not mTORC2, is associated with KA development, and the absence of pAkt<sup>Ser473</sup> could be related to its low invasive capacity, whereas the increase of pRPS6 would be related to the tumour differentiation pattern.

Based on our results, it is possible to conclude that PI3K Kinase p110 $\alpha$  and pAkt<sup>Ser473</sup> (mTOR2) enhanced activation are associated with more aggressive behaviour during lip carcinogenesis by triggering AC and LLSCC progression. Contrastingly, pRPS6 (mTOR1) seems to prevent tumour developments since its activity decreased during the progression of lip carcinogenesis.

### Acknowledgement

The authors are grateful to Flavia Rejane Giusti for her technical support and the Biostatistics Unit of the Postgraduate Research Group of the Porto Alegre University Hospital for assisting the statistical analysis. The authors are also grateful to the Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES-finance code 001), Brazilian National Council for Scientific and Technological Development (CNPq) and the São Paulo State Research Foundation (FAPESP 2016/21785-4) for student scholarships. This study was funded by the Postgraduate Research Group of the Hospital de Clínicas de Porto Alegre (GPPG/FIPE: 2018-0047). Manoela Domingues Martins and Pablo Agustin Vargas are research fellows funded by the Brazilian National Council for Scientific and Technological Development (CNPq).

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DOI: 10.1111/jdv.16420

## Poor prognosis of drug-induced and acute graft-versus-host disease-induced epidermal necrolysis in bone marrow/stem cell transplant recipients: a retrospective case series

### Editor

Toxic epidermal necrolysis (TEN) and stage IV acute graft-versus-host disease (AGVHD) are uncommon severe complications in bone marrow/haematopoietic stem cell transplant (BMT/HSCT) recipients and are often clinically indistinguishable.<sup>1–7</sup> We sought to identify discriminating clinical and pathological features between drug-induced EN (DI-EN) and acute graft AGVHDI-EN and determine their prognosis.

We retrospectively reviewed the charts of patients who underwent allo-BMT/HSCT at our institution from January 1997 to 2017 (IRB 16-029-MUHC). Patients were  $\geq 18$  years of age, underwent allo-BMT/HSCT and developed epidermal necrolysis, defined as detachment of full-thickness epidermis. To collate a