



CORRESPONDENCE

Aspects related to the inference of causality in cross-sectional studies. Comments on: '8-Hydroxy-2'-deoxyguanosine protein immunoexpression is associated with the pathogenesis of actinic cheilitis'[☆]

Dear Editor,

Due to the potential for malignancy and contiguity to the photoprotected mucosa, actinic cheilitis (AC) represents the archetype of the activity of the cutaneous field cancerization (CFC), an opportune model for research about carcinogenesis in *anima nobile*.¹ Therefore, the article by Varela et al., which explored the expression of 8-OHdG in AC, concluding for association with pathogenesis, was read with interest.² The authors should be congratulated; however, some comments related to the generalization of the results are essential.

The search for histopathological markers of CFC activity is relevant for its characterization, understanding of the pathogenesis, and to define outcome in therapeutic prospection. To date, no high-performance markers have been identified; however, the expression of p53, Ki67, detection of cyclobutane-thymidine dimers, and degree of epithelial dysplasia are the most studied ones.^{3,4}

While ultraviolet radiation induces oxidative stress in the epithelium and topical antioxidants reduce CFC activity, markers of oxidative damage in DNA are candidates for characterizing CFC activity.⁵ 8-OHdG expression is rapidly increased in sun-exposed epithelium, remaining for days after a radiation dose; however, it can also be induced by other oxidative agents, such as smoking and underlying inflammation.

Human skin is an organ which interacts with the environment and has, during evolution, developed DNA repair, apoptotic, and antioxidant mechanisms. Their failure justifies the higher incidence of neoplasms in syndromes (e.g.,



xeroderma pigmentosum), immunosuppressed patients, and the elderly. Lower lips are chronically exposed to the sun, justifying the regular expression of markers of oxidative damage. However, this study did not include a control group with healthy, photoexposed lips, nor was the photoprotected mucosa sampled, which would help in the comparative evaluation of 8-OHdG expression patterns.

The lack of association between the 8-OHdG histopathological score and the degree of AC dysplasia or smoking does not corroborate the expectation of a biological gradient. Moreover, the expression of 8-OHdG in AC, although intense, does not allow inferring that it is causally involved in the etiopathogenic process, or that it is a by-product of the epithelium with dysfunctional antioxidant mechanisms.

Finally, the nuclear and cytoplasmic expression of 8-OHdG must be analyzed separately, since damage to mitochondrial DNA induces autophagy, whereas nuclear damage is potentially carcinogenic. Although the authors declared that there was predominantly nuclear expression, but cytoplasmic too, there was no differential analysis, which makes the interpretation of these results difficult.

Therefore, the conclusion about the involvement of 8-OHdG in the pathogenesis of AC should be interpreted with caution.

Financial support

None declared.

Authors' contributions

Ivanka Miranda de Castro Martins: Design and planning of the study, drafting and editing of the manuscript; approval of the final version of the manuscript.

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Conflicts of interest

None declared.

[☆] Study conducted at the Department of Infectious Diseases, Dermatology, Imaging Diagnosis and Radiotherapy, Faculty of Medicine, Universidade Estadual Paulista, Botucatu, SP, Brazil.

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Received 7 March 2024

Available online 13 June 2024

<https://doi.org/10.1016/j.abd.2024.03.002>

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8-Hydroxy-2'-deoxyguanosine protein immunoexpression is associated with the pathogenesis of actinic cheilitis - Replay*



Dear Editor,

The authors appreciate the comments on their article: "8-Hydroxy-2'-deoxyguanosine protein immunoexpression is associated with the pathogenesis of actinic cheilitis" and would like to clarify some comments regarding the article.¹

When this study was carried out, the objective was to verify whether there was an association between 8-Hydroxy-2'-deoxyguanosine protein immunoexpression (8-OHdG) and the degree of morphological severity of actinic cheilitis (AC), since chronic exposure to ultraviolet radiation (UVR) is associated with the development and progression of AC to lip carcinoma. This fact led to the hypothesis that samples with higher degrees of dysplasia could harbor a higher expression of this protein. For this reason, cases of photoexposed healthy lips and photoprotected mucosa were not included in the sample. The inclusion of these two groups is suggested for further studies with comparison purposes with AC cases.

In relation to the sample patients who were smokers, it was not possible to observe a higher expression of 8-OHdG in the analyzed cases and this result may be due to the low percentage of smokers in the sample (7%).

According to the data from the present study, one cannot say that 8-OHdG can be used as a biological marker for the progression of AC to lip carcinoma. However, chronic exposure to UVR leads to the generation of reactive oxy-

gen species (ROS) and, consequently, to the formation of 8-OHdG, which can cause mutations in cell DNA.²

In this context, 8-OHdG has been used as a marker of carcinogenesis in several experiments, being well-established as a prognostic factor in esophageal cancer.³ It has also been observed that this protein is overexpressed in actinic keratosis and Bowen's disease lesions when compared to adjacent unaffected tissues, healthy controls and squamous cell carcinoma (SCC) samples.⁴

The expression of the 8-OHdG protein can be observed both in the nucleus and in the cytoplasm since the main source of ROS generation is the mitochondria. This process leads to the oxidation of biomolecules, with consequent homeostatic cell imbalance, resulting in the development of several diseases such as atherosclerosis, diabetes, neurodegenerative disorders and cancer.^{3–5} Although the present study did not perform a differential analysis between nuclear and cytoplasmic levels of 8-OHdG, one can say, based on the literature, that increased levels of this protein may be related to the pathogenesis of AC.

Financial support

None declared.

Authors' contributions

Cíntia Barreto de Oliveira Varela: Data collection, analysis and interpretation; Critical literature review; Preparation and writing of the manuscript, approved the final version of the manuscript.

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