

Involvement of olfactory receptor OR2AT4 in skin aging and the response to environmental pollution

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Introduction

The olfactory receptors (ORs) belong to the 7-transmembrane G protein-coupled receptors family, expressed in the olfactory epithelium and mediate the odor perception [1]. Among 400 ORs are known in human, their expression has been evidenced in various peripheral tissues such as skin. Among the ORs described in the skin, OR2AT4 is detected in keratinocytes, melanocytes, dendritic cells, and hair follicles. The activation of OR2AT4 has been linked to downstream effects on cell proliferation, migration and re-epithelialization associated with wound healing [2]. Other studies mentioned the involvement of ORs in the chemosensory perception and the sensing of skin bacterial colonization [3]. However, the roles of ORs in the skin, and precisely of OR2AT4, are still incompletely described, in particular their possible involvement in the detection of pollution and in aging.

Methods

In this study, OR2AT4 expression was investigated in various senescent skin models *in vitro*. Moreover, an extract of *Santalum album*, selected by bioinformatic studies for its ability to modulate the expression of OR2AT4, was evaluated.

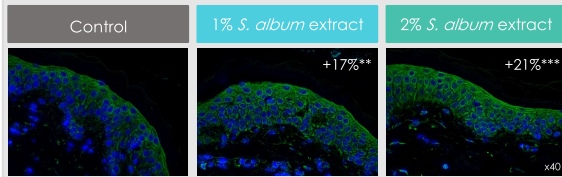
Besides, the consequences of ultrafine particle-induced skin damage were studied via the evaluation of OR2AT4 expression level and markers involved in skin senescence and differentiation.

Results

Modulation of OR2AT4 by an extract of *Santalum album*:

In this study, we evaluated an extract of *Santalum album*, selected by bioinformatic studies for its ability to modulate the expression of OR2AT4 and related markers.

OR2AT4 expression in *ex vivo* skin treated with *S. album* extract for 48 h

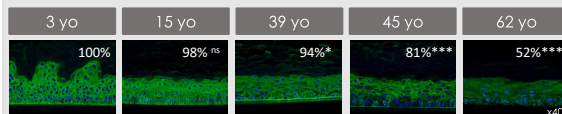


A significant increase of OR2AT4 protein level was associated with 48 h application of 1% or 2% *S. album* extract, on *ex vivo* skin biopsies.

Expression of OR2AT4 in skin aging:

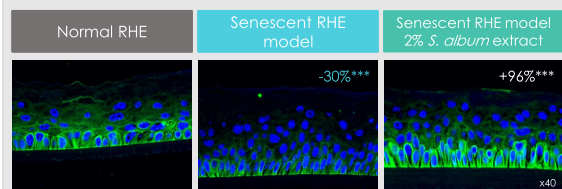
The modulation of OR2AT4 was observed in RHEs obtained from donors of various age. A significant decrease of OR2AT4 protein level was observed in RHE when the age of the donor increased.

OR2AT4 expression in RHEs from donors of various age



To confirm this result, a senescent RHE model, induced by FOXO3 downregulation, was used.

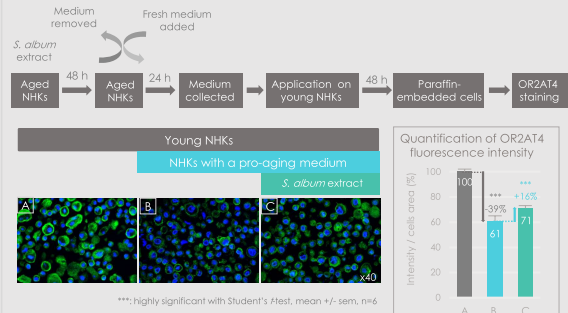
OR2AT4 expression in senescent RHE model treated with *S. album* extract for 48 h



A significant decrease of OR2AT4 protein level was observed in senescent RHEs. When senescent RHEs were treated with *S. album* extract, the lowering of the OR2AT4 protein was limited.

In parallel, normal human keratinocytes (NHKs) from young donor (young NHKs) were cultured in pro-aging environment, a conditioned medium from adult donor (aged NHKs).

OR2AT4 expression in NHKs cultured in a pro-aging environment



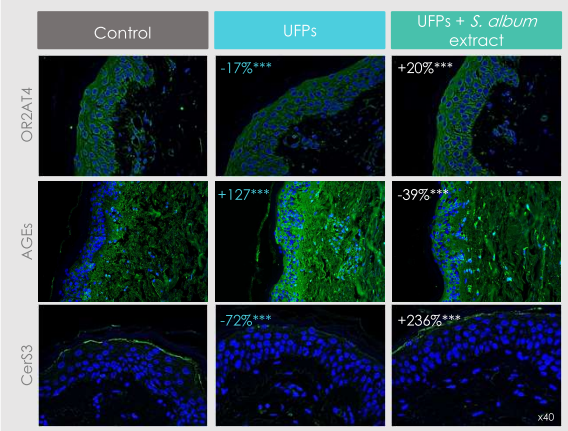
A significant decrease of OR2AT4 protein level was observed when young NHKs were cultured in pro-aging environment. When *S. album* extract is added, the decrease of OR2AT4 protein expression observed in young NHKs cultured in pro-aging medium, was limited.

Effect of the environmental pollution on OR2AT4 level

Urban air pollutants are the major extrinsic factors promoting skin aging. In this study, we used ultrafine particles (UFPs) from diesel exhaust to evaluate the impact of environmental pollution on OR2AT4 level.

In addition, advanced glycation ends products (AGEs), compounds which accumulate in extrinsically aged skin, and ceramide synthase 3 (CerS3), a marker of skin barrier function, were investigated.

OR2AT4, AGEs and CerS3 expressions in *ex vivo* skin stressed by UFPs for overnight and treated with *S. album* extract for 48 h



The expressions of OR2AT4, AGEs and CerS3 were modulated in *ex vivo* skin stressed by UFPs. When *ex vivo* skin was treated with *S. album* extract, the expression of OR2AT4 and CerS3 came back to initial basal level and AGEs content was limited.

Conclusion

Our results showed that the expression of OR2AT4 was inversely correlated with aging and UFPs-induced skin damage, suggesting that its modulation could be beneficial to limit the consequences of intrinsic and extrinsic aging into the skin.

References

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- 3-Thom EH, et al. (2019) Expression and function of the ectopic olfactory receptor OR10G7 in patients with atopic dermatitis. J Allergy Clin Immunol. 143(5):1838-1848.