

Unique epigenetic modulation by EPIT compared to OIT in a model of peanut sensitized mice: sustainable GATA-3 hypermethylation and Foxp3 hypomethylation

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Background: Epicutaneous immunotherapy (EPIT) is a safe treatment for food allergy. In animal models, EPIT protection seems to be more sustained compared to oral immunotherapy (OIT) and prevents further sensitization. This study investigates the kinetics of epigenetic modifications underlying the therapeutic effect of EPIT, its persistence and its bystander effect.

Method: BALB/c mice were orally sensitized to peanut and then treated with EPIT or OIT or non-treated. Mice were sacrificed during treatment at 1, 2, 4, 6 and 8 weeks; and 8 weeks after the end of treatment. A set of peanut-sensitized mice were sacrificed following exposure to a protocol of sensitization to a new allergen, OVA. DNA methylation was analysed in sorted CD4⁺ cells from spleen and blood by pyrosequencing.

Results: In spleen and blood CD4⁺ cells, a significant hypermethylation of the CpG island associated with the Gata3 promoter occurred at the 4th week of EPIT ($p < 0.05$), persisted until the end of treatment ($p < 0.05$ and $p < 0.01$, respectively) and was sustained after the end of the treatment ($p < 0.01$). This change was not observed for mice treated with OIT. A significant hypomethylation of the Foxp3 CpG island was concomitantly observed in spleen and blood CD4⁺ T cells, persisting until the end of EPIT ($p < 0.01$) and sustained off treatment ($p < 0.05$). For OIT, hypomethylation reached a level similar compared to EPIT only in spleen CD4⁺ T cells and was not sustained off treatment. Interestingly, mice treated with EPIT and protected from the sensitization to OVA as a new allergen, maintained the epigenetic signature characteristic for EPIT, i.e. Gata3 hypermethylation ($p < 0.05$) and Foxp3 hypomethylation ($p < 0.05$) in spleen and blood. No modification was observed for the Tbet and ROR γ transcription factors whatever the cells, organs or treatment protocol.

Conclusion: EPIT, as compared to OIT, leads to a unique and stable epigenetic signature with downregulation of Th2 DNA expression and upregulation of Treg transcription factors, likely explaining the sustainability of the protection and its bystander effect.