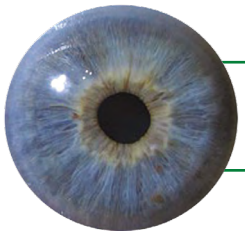

Visión del autor

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Allergoid-mannan conjugates reprogram monocytes into tolerogenic dendritic cells via epigenetic and metabolic rewiring

Cristina Benito-Villalvilla[1]; Mario Pérez-Diego[1]; Alba Angelina[1]; Kai Kisand[2]; Ana Rebane[2]; José Luis Subiza[3]; Oscar Palomares[1]

[1]Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University, Madrid, Spain [2]Institute of Biomedicine and Translational Medicine, University of Tartu, Estonia; [3]Inmunotek, Alcalá de Henares, Madrid, Spain

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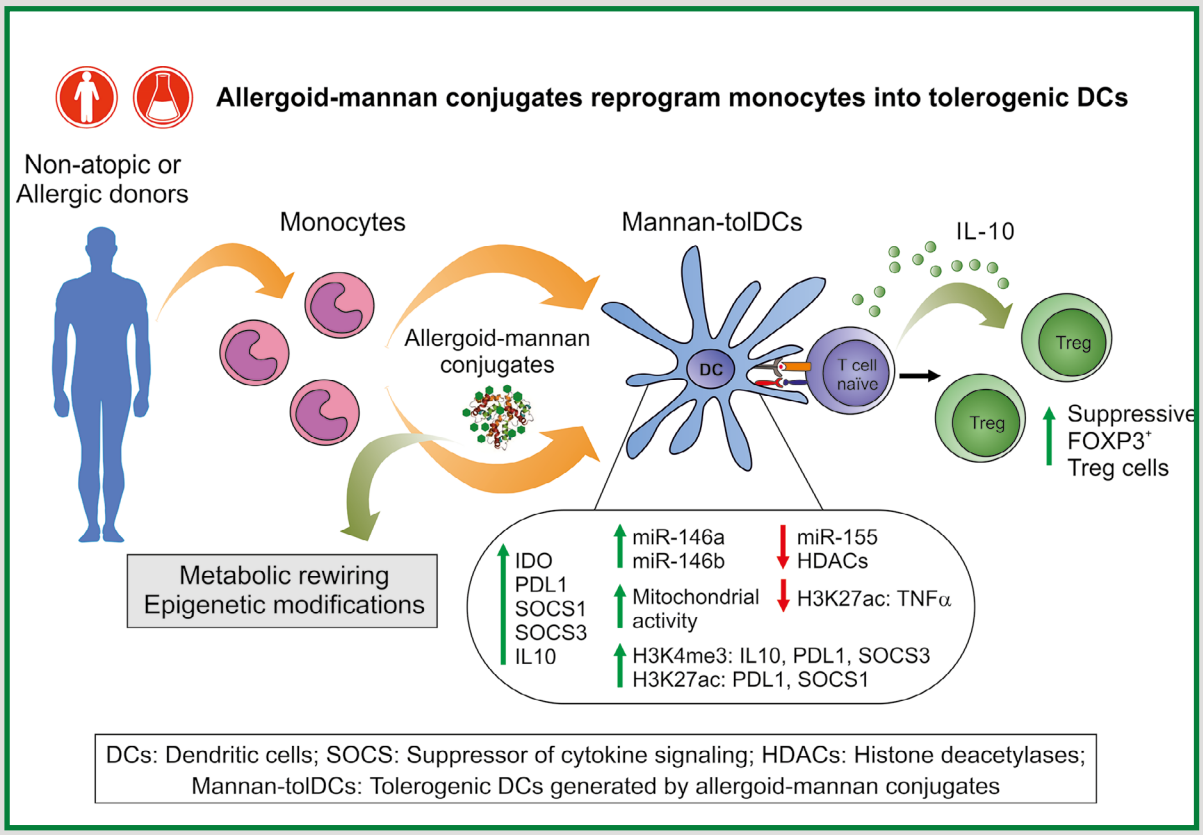
Allergen-specific immunotherapy (AIT) is currently the only disease-modifying treatment with potential curative capacity for allergy. Glutaraldehyde-polymerized allergoids conjugated to nonoxidized mannan (Allergoid-mannan conjugates) are next-generation vaccines for AIT being currently assayed in phase 2 clinical trials. Allergoid-mannan conjugates target dendritic cells (DCs) and generate functional



forkhead box P3 (FOXP3)$^+$ regulatory T (Treg) cells, but their capacity to reprogram monocyte differentiation remained unknown. Therefore, we decided to study whether allergoid-mannan conjugates could reprogram monocyte differentiation into tolerogenic DCs and the underlying molecular mechanisms. For that, we purified monocytes from nonatopic donors and allergic subjects, differentiated them in the presence or absence of the vaccine and studied the underlying epigenetic and metabolic reprogramming events taking place in the assayed conditions.

As shown in the graphical abstract, we observed that monocyte differentiation from non-atopic and allergic subjects into DCs in the presence of allergoid-mannan conjugates yields tolerogenic DCs (Mannan-DCs) characterized by a lower cytokine response to LPS stimulation, a higher expression of the tolerogenic molecules *PDL1, IDO, SOCS1*, *SOCS3* and *IL10*, and a higher capacity to induce functional FOXP3$^+$ Treg cells than conventional DCs. Mannan-DCs shift their metabolism from Warburg Effect and lactate production towards a higher mitochondrial oxidative phosphorylation, and display epigenetic reprogramming with lower levels of histone deacetylases genes (HDACs), specific histone marks within tolerogenic loci, higher expression of the anti-inflammatory miRNA-146a/b and lower expression of the pro-inflammatory miRNA-155. This study shed light into the capacity of allergoid-mannan conjugates, a novel AIT vaccine, to induce a tolerized innate memory state in human DCs, which might well pave the way for the design of new generation therapies and vaccines for allergy and other immune-mediated diseases.

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Por Cristina Benito-Villalvilla
Department of Biochemistry and Molecular Biology, School of Chemistry, Complutense University, Madrid, Spain
cribenit@ucm.es