Characterization of the primary uptake pathway for tolerogenic allergen-specific virus-like particles by antigen-presenting cells and approaches for its modulation

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Abstract text

Text: **Background**

Virus-like nanoparticles (VNP) are considered efficient vaccination platforms and have been shown to be useful to enable non-anaphylactogenic delivery of allergen-specific immunotherapy in preclinical models. However, the mode of VNP uptake by antigen presenting cells (APC) remains unclear.

Methods

Accordingly, we screened a collection of substances known to inhibit distinct uptake pathways in APC. The human monocytic leukemia cell line THP-1 and the murine dendritic cell line DC 2.4 were examined for the uptake of fluorescently labelled VNP in the presence or absence of inhibitors. Candidate-substances that blocked VNP uptake in APC lines were subsequently evaluated in studies with primary APC present in splenocyte and lung cell homogenates *in vitro* and upon intratracheal application of VNP *in vivo*.

Results

Uptake of allergen-specific VNP *in vitro* and *in vivo* was mainly detected in macrophages and $CD103^+$ DCs and was sensitive to macropinocytosis-inhibitors, such as hyperosmolar sucrose or the polyphenolic compound Rottlerin at low micromolar concentrations, but not to other inhibitors. In addition, T-cell proliferation induced by allergen-specific VNP was significantly reduced in the presence of Rottlerin, without any change in MHC expression levels. In contrast, substances that stimulate macropinocytosis, such as Heparin and phorbol myristate acetate, increased VNP-uptake and could thus contribute to the modulation of allergen-specific T-cell responses.

Conclusion

We have identified macropinocytosis as the major uptake mechanism of APC for allergen-specific VNP *in vitro* and *in vivo*, paving the way for further improvement of VNP-based therapies, especially those that can be used for tolerance induction in allergy in the future.

Conflict of Interest statement

Do you have any conflict of interest to declare?: Yes

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Affirmation

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