Candida albicans quorum sensing molecule Farnesol modulates human dendritic cells function by nuclear receptors activation

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Introduction

The quorum sensing molecule farnesol mediates the response of *Candida albicans* to growing population and controls filamentation in this fungus. Moreover, farnesol interacts with host immune cells such as neutrophils, macrophages and dendritic cells. This molecule impairs differentiation of monocytes into dendritic cells (DCs); nevertheless, the molecular mechanisms underlying these effects are not known. In this project, we aim to elucidate potential mechanisms involved in the farnesol-mediated effects on DCs differentiation.

Methods

Monocytes were differentiated into dendritic cells with GM-CSF and IL-4 for 6 days, in presence or absence of farnesol (50 μ M), and agonists and antagonists for PPAR γ and RAR α nuclear receptors.

- Immunophenotype characterization of DCs by FACS
- Transcriptional analysis of farnesol-mediated DCs differentiation
- iNKT proliferation by DCs through FACS
- Cytokines release by a multiplex immunoassay

Results

1. Farnesol increases the expression of genes associated with nuclear receptors pathway

Transcriptional analysis of farnesol-mediated DCs differentiation revealed a high number of differentially regulated genes involved in the nuclear receptors PPAR γ and RAR α pathways. Nuclear receptors are involved in dendritic cells differentiation.

3. Farnesol impairs antigen-presenting and costimulatory molecules expression through the PPAR γ -RAR α axis

DCs differentiated in presence of farnesol showed impaired expression of costimulatory and antigen-presenting molecules. The presence of antagonists for nuclear receptors blocked farnesol effects on CD1d, CD86 and CD80 but not CD1a.

2. Farnesol activates PPAR γ and RAR α

Farnesol treatment increases the expression of *FABP4* and *TGM2*, which are in control of PPAR γ and RAR α respectively

4. iNKT specific expansion by farnesol-treated DCs

Upregulation of CD1d molecules in dendritic cells is associated with an increase capacity to activate invariant Natural Killer T (iNKT) cells.

Farnesol-DCs have a high expression of CD1d; nevertheless, these cells have a lower capacity to induce iNKT proliferation after 7 days of co-culture with autologous T-cells. Pre-treatment with PPAR γ antagonists partially restored their capacity to prime iNKT.

5. Production of cytokines by DCs differentiated with farnesol

Farnesol treatment impaired cytokines secretion by DCs after stimulation with LPS independent on the PPAR γ pathway.

Conclusion

We found that farnesol promotes transcriptional rewiring that leads to an impaired phenotype in DCs. In particular, CD1d expression was increased and dependent on the PPAR γ -RAR α axis; nevertheless, these cells have a decreased capacity to activate iNKT. Furthermore, farnesol-DCs showed impaired production of T-cell inducing cytokines. Further experiments will be performed to elucidate alternative pathways involved in farnesol-treated DCs.