Usefulness of myeloid dendritic cells in cellular in vitro assays for evaluating immediate hypersensitivity reactions to betalactams

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Introduction
Dendritic cells (DCs) are the most potent antigen presenting cells (APCs) with an important role detecting, processing, and presenting antigens to T cells. The analysis of expression of migration, maturation, and activation markers on their surface after in vitro stimulation with the culprit drug, and their ability to trigger the proliferation of specific T cell populations in patients with immediate drug hypersensitivity reactions (IDHRs) could serve to prove the sensitization to a drug. Most approaches used monocyte-derived DCs (moDCs), although their sensitivity is not optimal. The different nature of moDCs and myeloid DCs (mDCs), main DC population involved during the in vivo development of IDHRs, could influence the sensitivity of these in vitro tests. Therefore, we evaluated the effect of two betalactams (BLs), amoxicillin (AX) and clavulanic acid (CLV) in moDCs and mDCs from selective-allergic patients (AP) to each BL, as well as to assess their capacity to stimulate different T cell populations.

Methods
mDCs and moDCs were obtained from 14 AX-AP, 14 CLV-AP and 10 Healthy controls (HC). After stimulating with the culprit BL, the expression of CCR7, CD40, CD80, CD83, and CD86 was assessed by flow cytometry. Their capacity to stimulate different T cell populations (CD3+T, CD8+T, and CD4+T cells, with a Th1 and Th2 cytokine pattern) was assessed by flow cytometry. T cell proliferation results were compared with the traditional approach, based on the direct stimulation of peripheral blood mononuclear cells with the culprit drug.

Results
Higher expression of CCR7, CD40, CD80, CD83, and CD86 was observed in both AX- and CLV-AP compared with HC when using BL-stimulated-mDCs, whereas with moDCs, only higher expression was observed in AX-AP, but not in CLV-AP. The % of positive maturation cases was higher with mDCs than moDCs, independently the BL involved, although higher % was obtained after stimulation with AX compared to CLV. The most relevant T cell population proliferative response was obtained in CD4+Th2 cells, reaching to 67% of positivity when using mDCs, followed by 50% with the traditional LTT, and only of 22% with moDCs from AX-AP. In CLV-AP, the % of positivity was of only 25% with mDCs, 20% with moDCs and 0% with PBMCs. The specificity was higher than 80% in all cases. The inclusion of mDCs in LTT allowed to completely differentiate between the elicitor drug which cause the reaction from related drugs, whereas both the inclusion of moDCs and the traditional LTT did not completely allow to differentiate between them.

Conclusions
mDCs from selective AP efficiently recognised the culprit drug and triggered the proliferation of T-cells, mainly those with a Th2 cytokine pattern, although these responses depended on the drug.

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