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Human autologous tolerogenic dendritic cells impair T-cell proliferation through contact-independent mechanisms

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Background

Autologous tolerogenic dendritic cells (ATDC) have been demonstrated to be able to increase heart, skin and pancreatic islet allograft survivals in murine models and to be safe in non-human primates. Due to their efficacy and their safety, ATDC therapy has been moved to clinic in a first phase I/II clinical trial in kidney transplantation in the context of the ONE study project. Human ATDC are generated from elutriated monocytes cultured 6 days in AIMV medium supplemented with low dose of GM-CSF. After differentiation ATDC display a tolerogenic dendritic cell profile (i.e. they display an immature phenotype, they express immunomodulatory cytokines such as IL-10 and TGF- β , they are resistant to maturation and they have suppressive activity toward T-cells). This project aims to determine the suppressive mechanisms of human ATDC toward T-cells.

Model

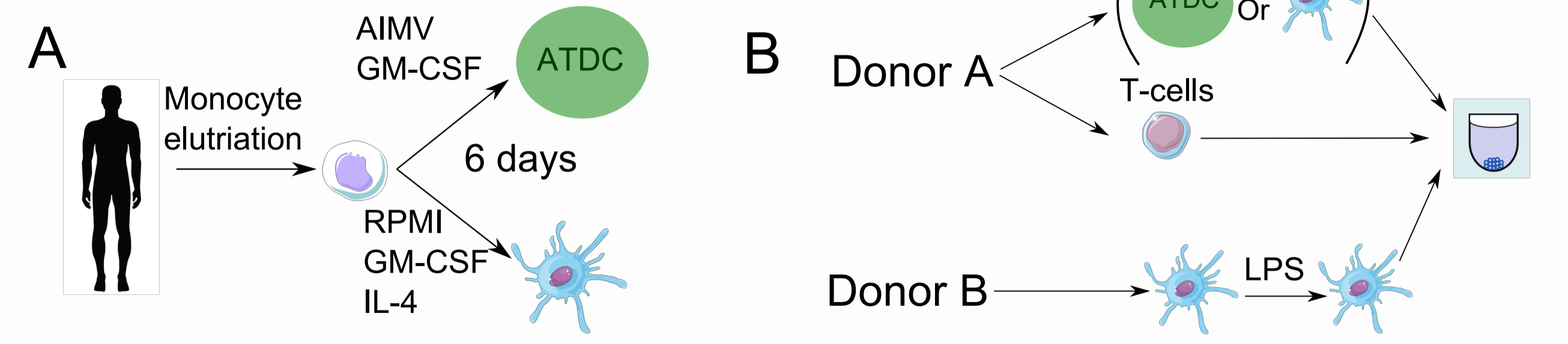


Figure 1. (A) Schematic representation of ATDC and MoDC differentiation. In this study we used MoDC as control cells. **(B)** Model of suppression assay used in this study. CD4⁺T-cells are cultured with allogeneic mature dendritic cells (mDC) with or without ATDC or MoDC (autologous to CD4⁺ T-cells)

ATDC impair CD4⁺ T-cell proliferation through contact independent mechanisms

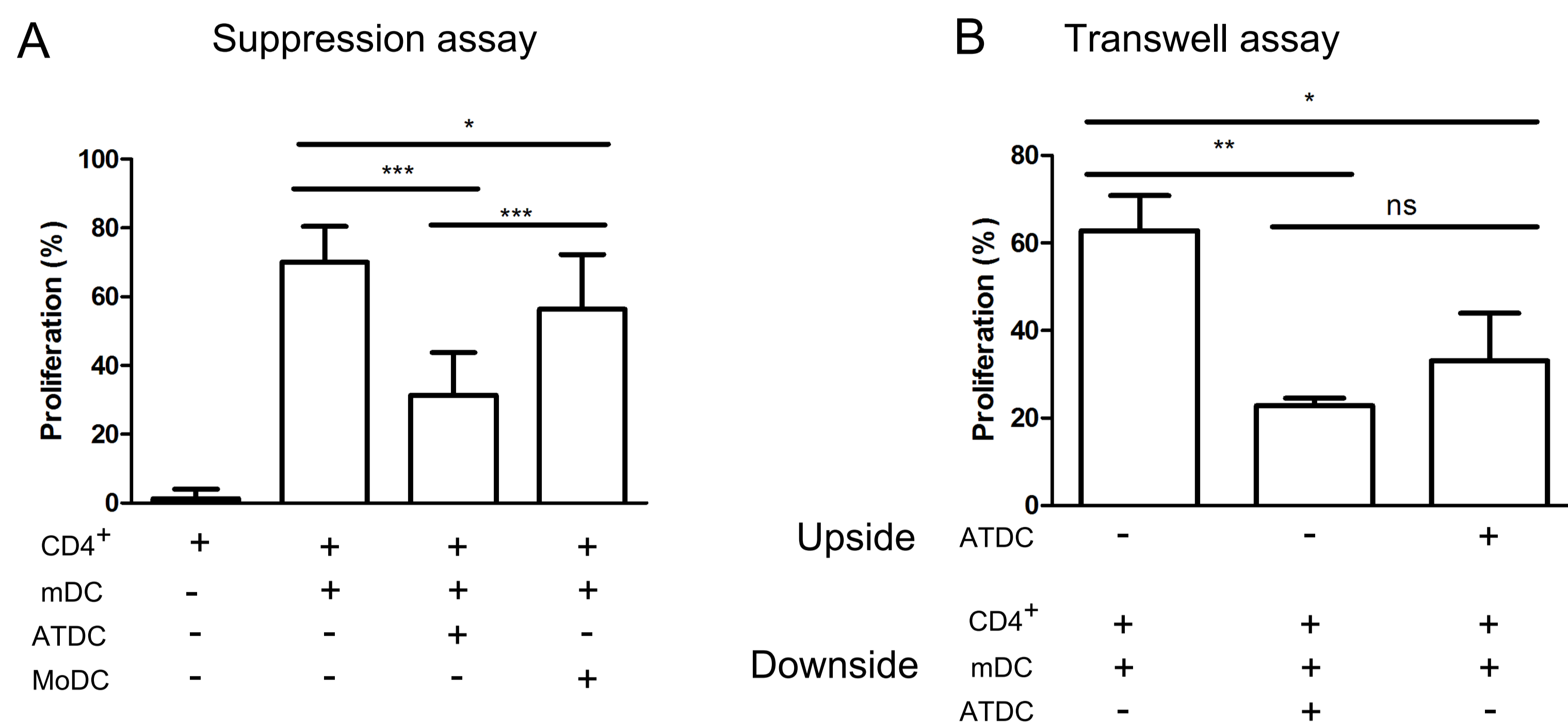


Figure 1. (A) CD4⁺ T-cell proliferation in suppression assay and **(B)** transwell assay

ATDC impair Th1 and Th17 proliferation while promote Treg

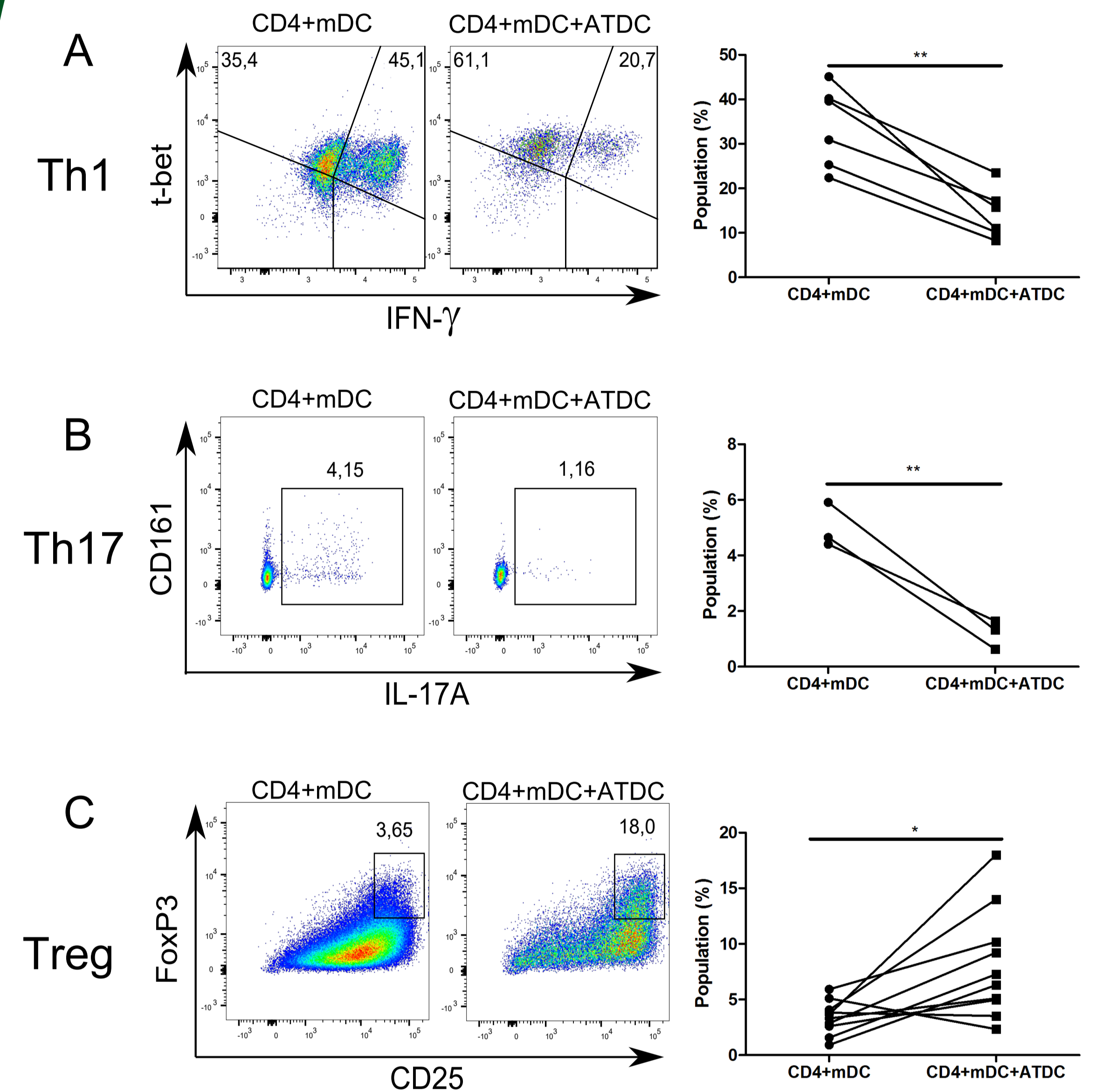


Figure 3. (A) Percentage of proliferating CD4⁺t-bet⁺IFN- γ ⁺ Th1 cells, **(B)** CD4⁺IL17A⁺ Th17 cells, and **(C)** CD4⁺CD25^{hi}FoxP3^{hi} Treg cells after suppression assay

ATDC impair CD4⁺T-cell proliferation through G0/G1 phase blockade without inducing apoptosis nor anergy

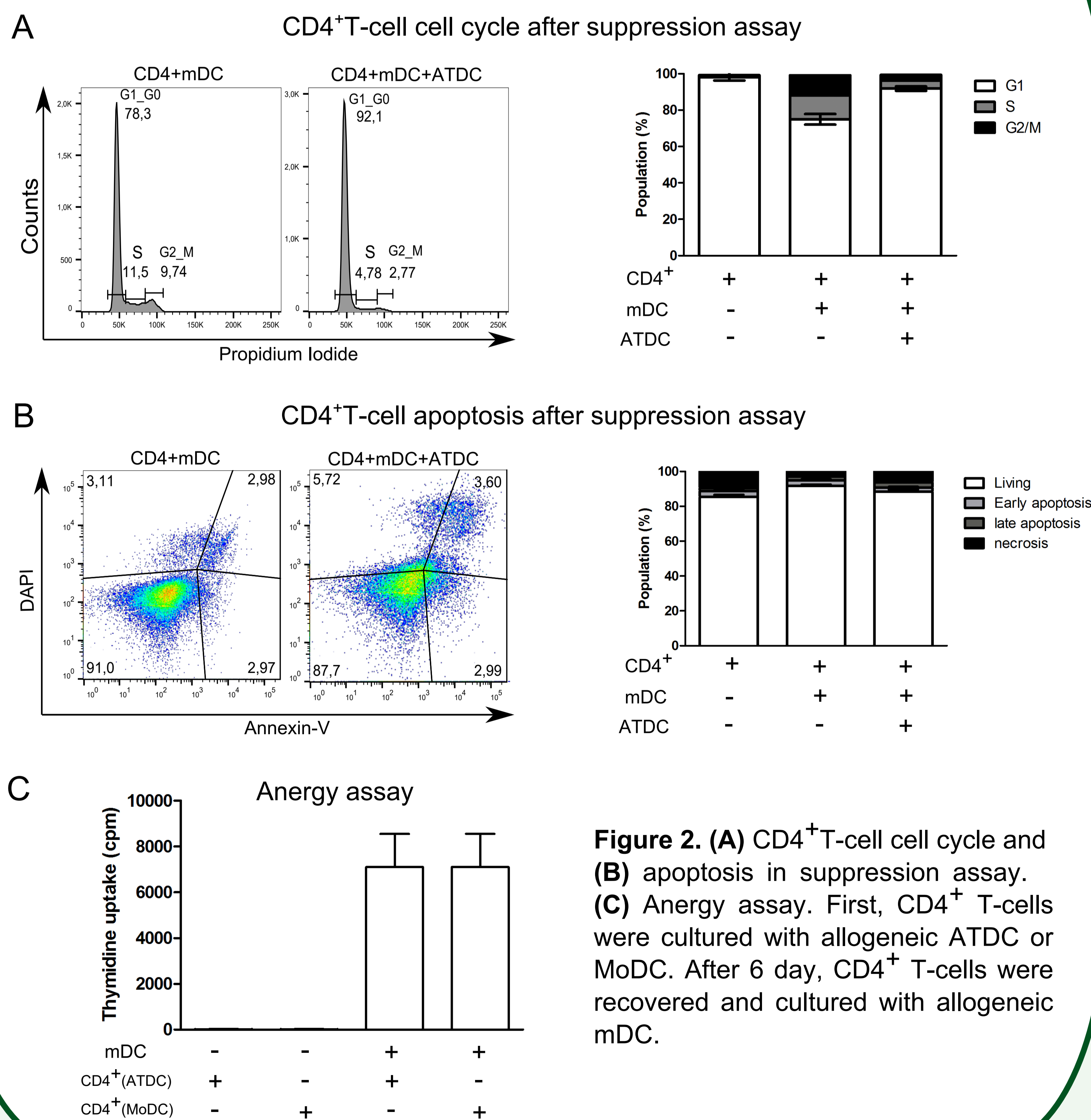


Figure 2. (A) CD4⁺T-cell cell cycle and **(B)** apoptosis in suppression assay. **(C)** Anergy assay. First, CD4⁺ T-cells were cultured with allogeneic ATDC or MoDC. After 6 day, CD4⁺ T-cells were recovered and cultured with allogeneic mDC.

ATDC induce the generation of "de novo" Treg partially through the production of TGF- β

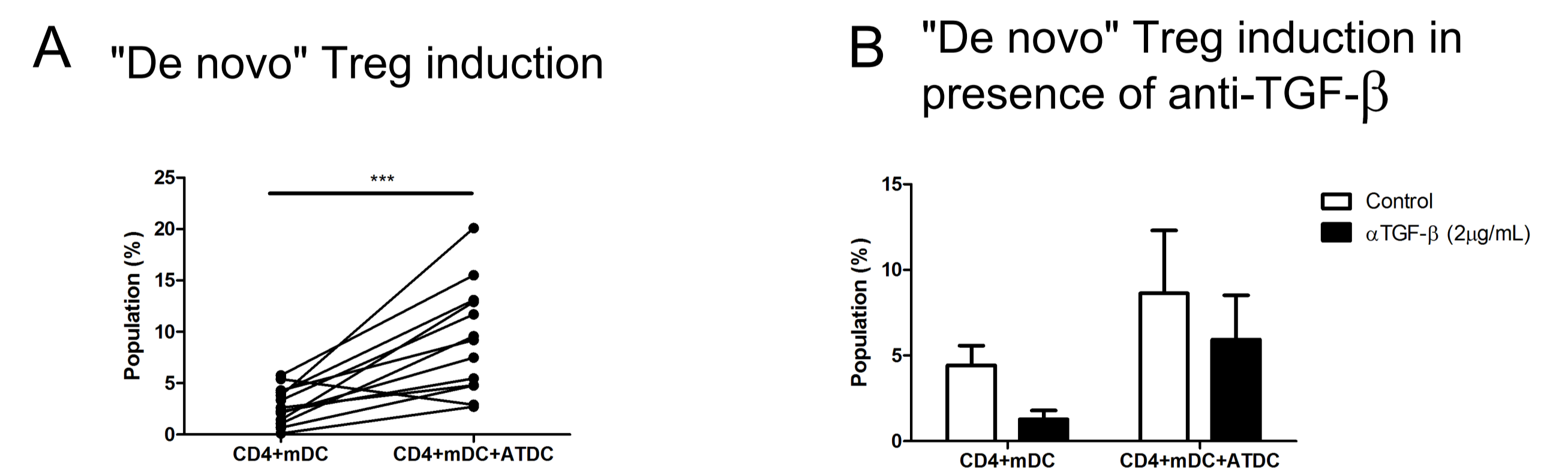
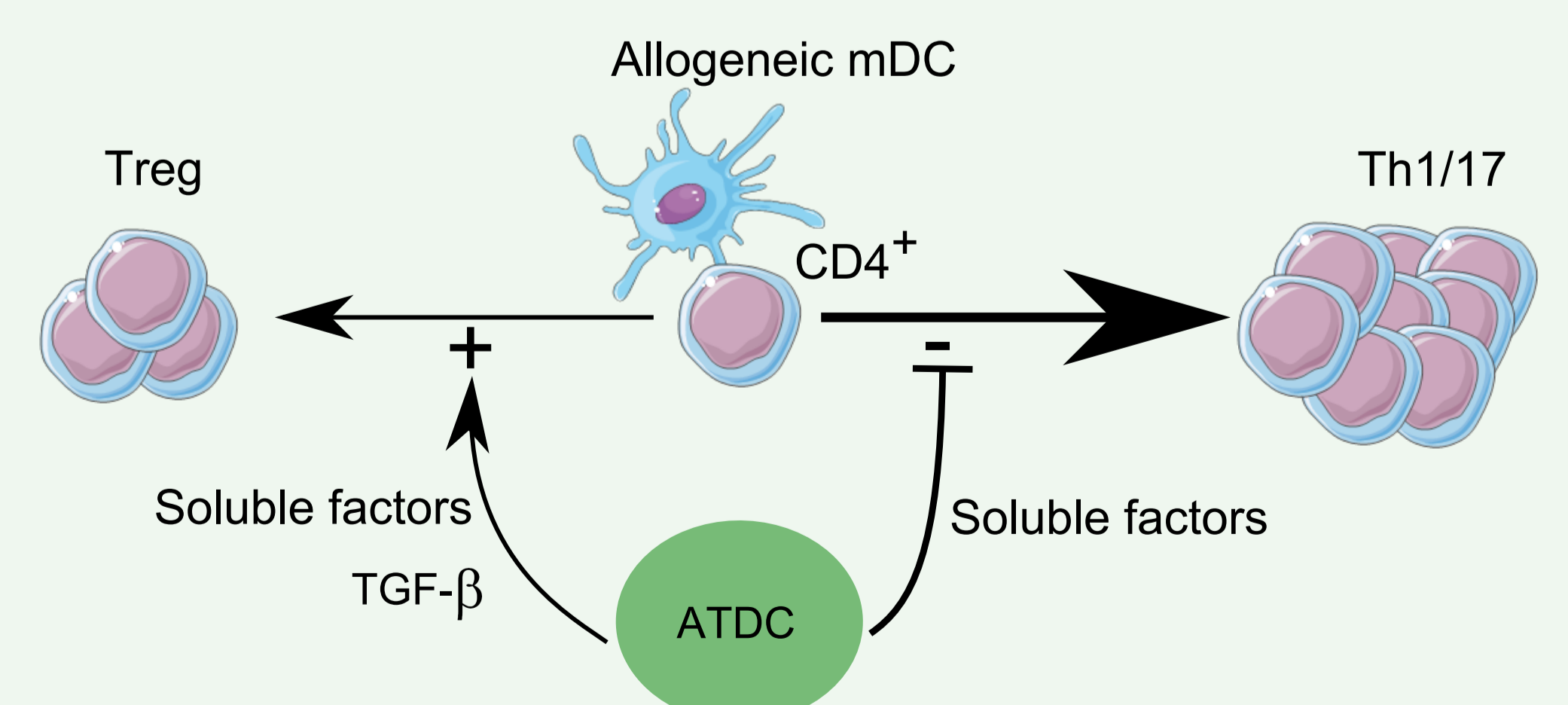


Figure 4. (A and B) Suppression assay starting with CD4⁺CD25⁻ T-cells instead of total CD4⁺ T-cells. **(A)** Percentage of proliferating CD4⁺CD25^{hi}FoxP3^{hi} Treg cells and **(B)** after adding TGF- β blocking antibody.

Conclusion



These results altogether showed that low dose GM-CSF-induced ATDC are able to suppress CD4⁺T-cell proliferation and to induce "de novo" Treg in part through the expression of TGF- β . Moreover we evinced that ATDC impair T-cell proliferation by contact-independent mechanisms without association with apoptosis nor anergy but with the blockade of cell cycle in G0/G1 phase. In-depth investigations will be performed to determine the molecular mechanisms underlying ATDC.