

GZMB+ B cells, a key factor of cell immunity in human?

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1-INTRODUCTION

Accumulating evidences show the existence of B-cells able to exert suppressing activities (Bregs) through different mechanisms. We report on an increase of a specific B cell population with suppressive regulatory functions in the blood of transplanted patients with long-term graft outcome.

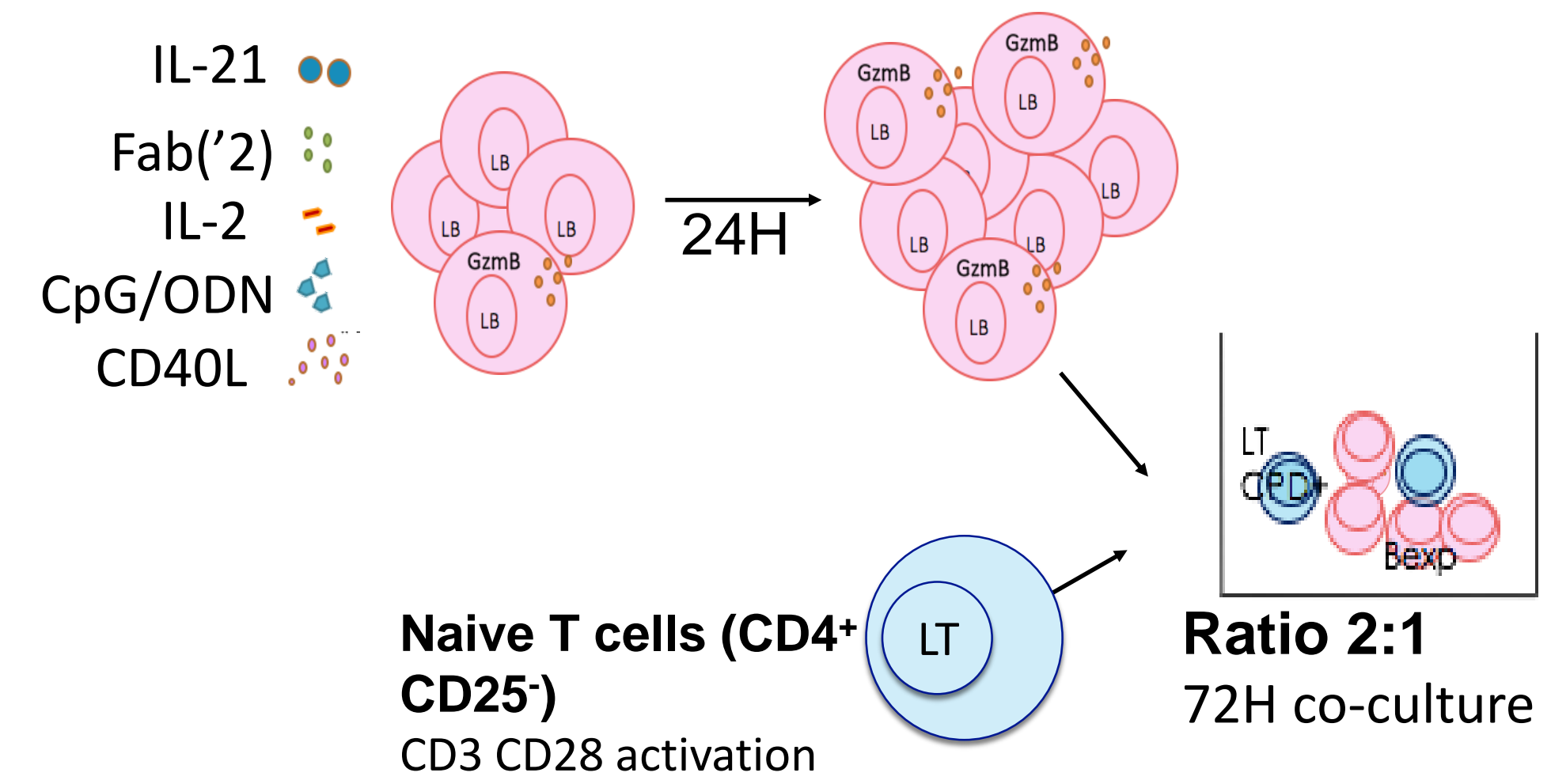
These B cells inhibit an effector T cell response through a granzyme B (GZMB⁺) dependent mechanism. We showed that such a population is present in healthy volunteer likely participating to a complex homeostasis cell orchestra and key regulator of immune response in chronic inflammation.

The aim of our study is to characterize their phenotype, their mode of action and we propose a method to induced them for future cell therapy.

2-MATERIAL AND METHODS

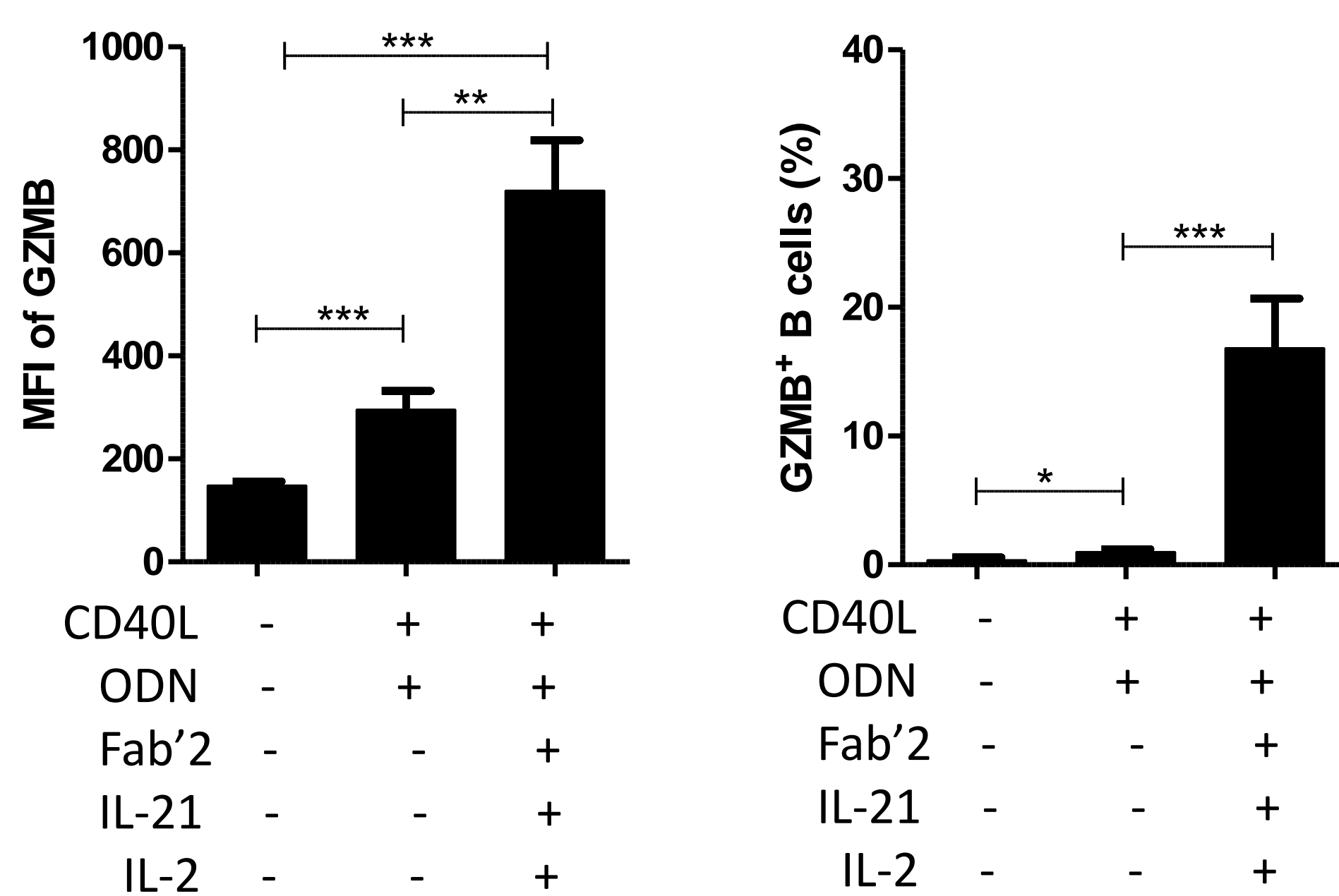
PBMCs from Heathy volunteers => B cells isolation (negative selection)

- GZMB⁺ B cells induction
- Analysis of regulatory function

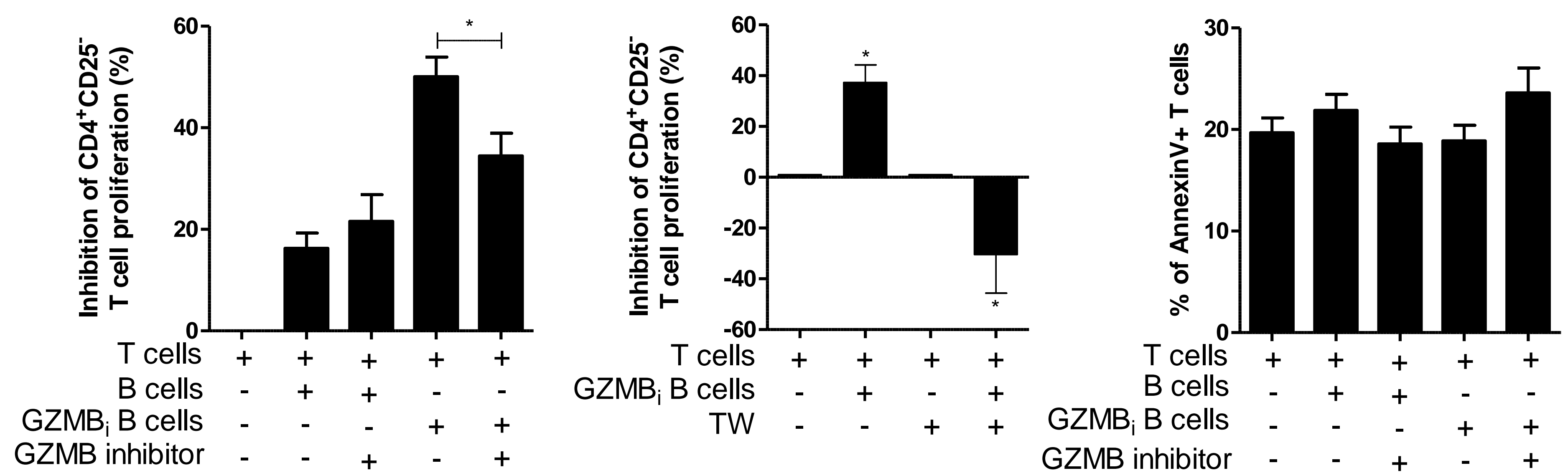


3- RESULTS

1- In vitro GZMB⁺ B cells induction



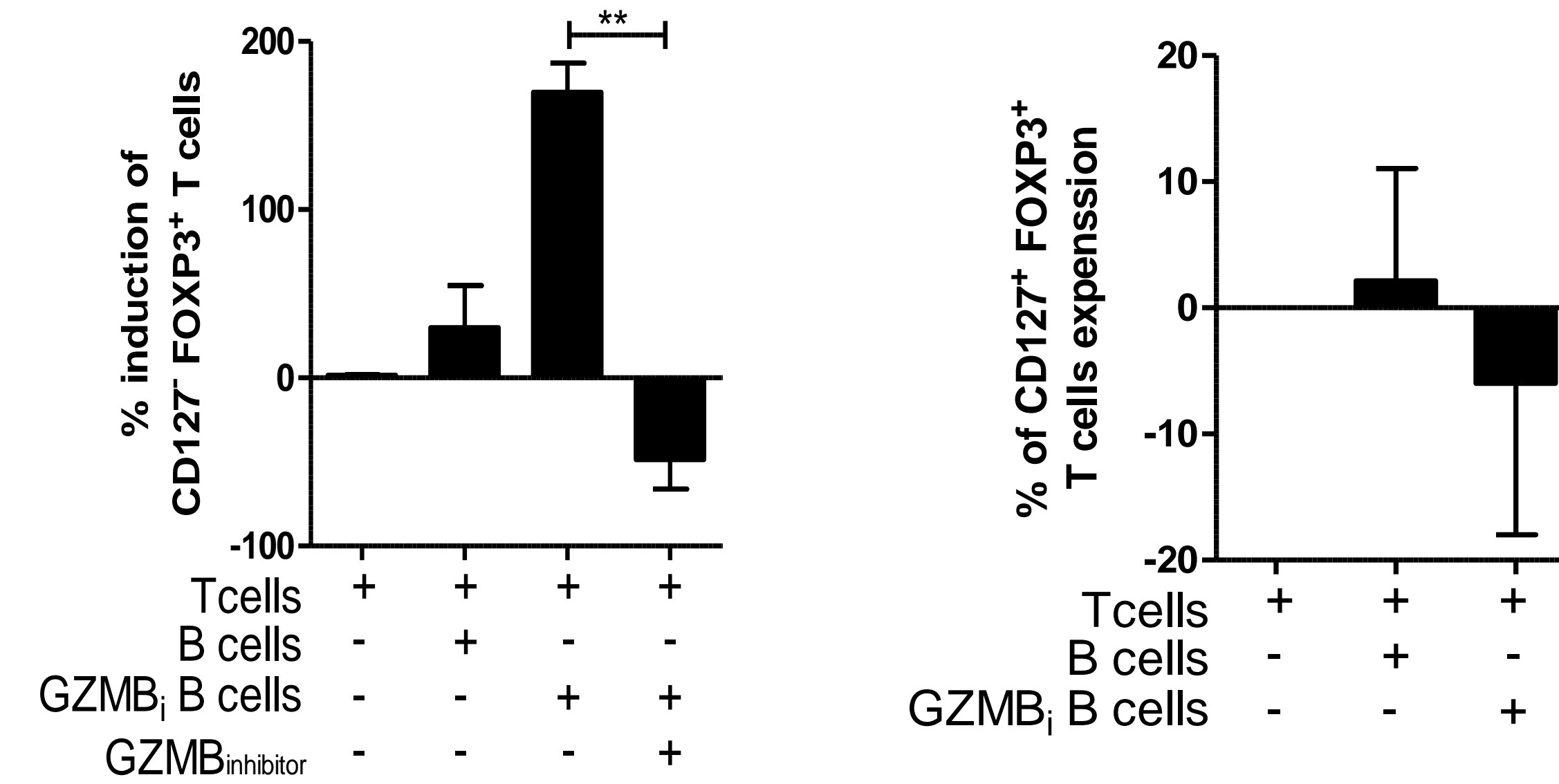
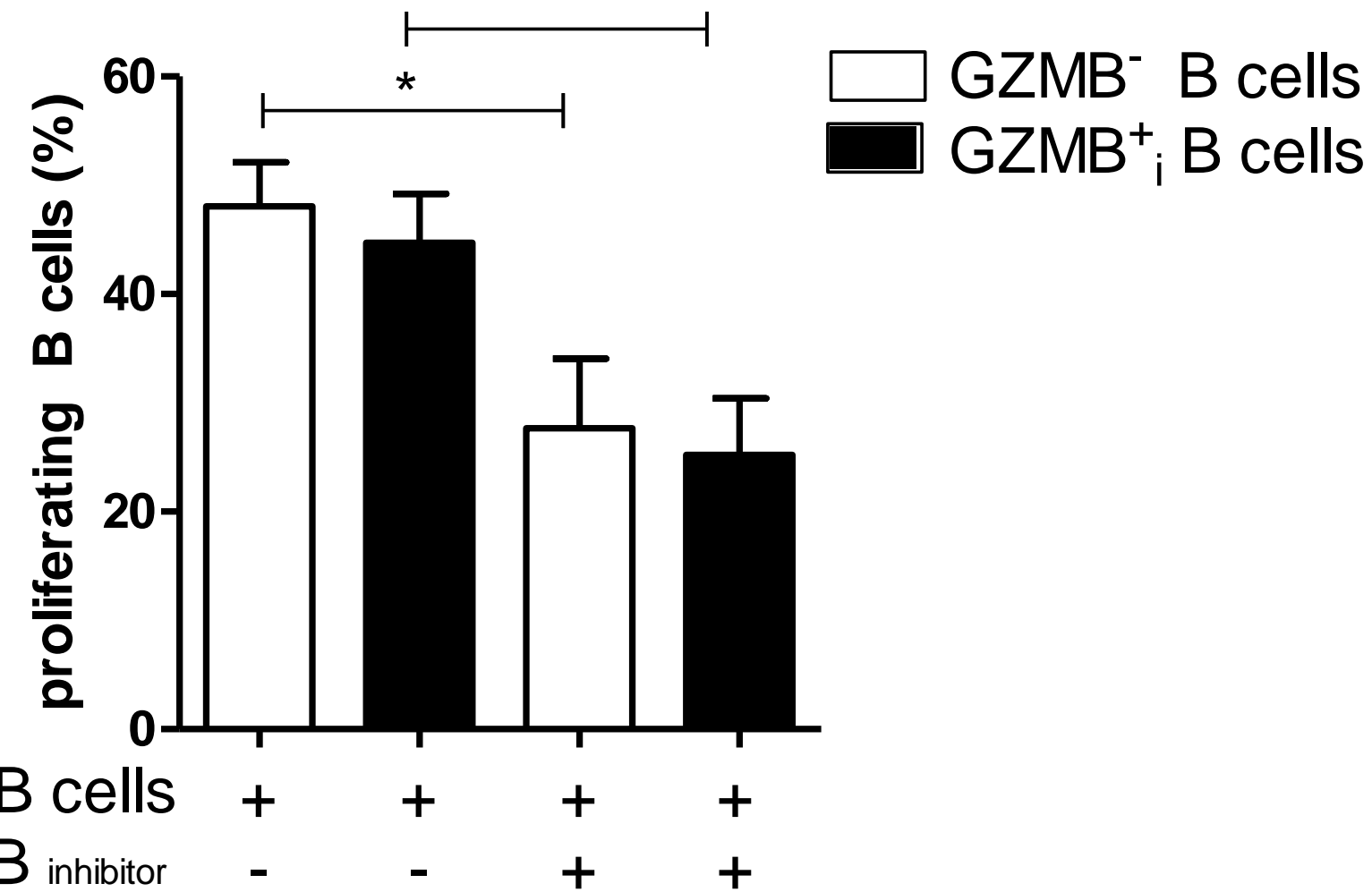
2- Regulatory function of induced GZMB⁺ B cells



Around 17 % of GZMB⁺ B cells were induced (GZMB⁺_i B cells) after 3 days culture with CD40L, ODN, Fab'2, IL-21 and IL-2.

GZMB⁺_i B cells inhibits effector T cells proliferation higher than non induced GZMB⁺ B cells in GZMB and contact dependent manner, without inducing T cells apoptosis.

3- Homeostasis of GZMB⁺ B cells



Addition of GZMB inhibitor in 3 days culture prevents B cell proliferation suggesting that GZMB secreted by GZMB⁺_i B cells concurs to their own proliferation.

After coculture with effector T cells, GZMB⁺_i B cells induces T cells with regulatory function in a GZMB dependent manner.

4-CONCLUSION

We identified Breg cells with a dual regulatory role, both blocking conventional T cell proliferation and inducing Treg cells but also maintaining cell homeostasis. These data evidence that GZMB⁺ B cells are tightly regulated through a feed back loop control of proliferation and death suggesting a fine control of these cells able to maintain a physiological T cell response in healthy volunteers.

We identified an efficient induction protocol for Bregs with stable suppressive activity.

These data provide new insights into the GZMB⁺ B cell biology and function as well as new clues for novel future therapies in inflammatory diseases and cancers.