Diminished PD-L1 upregulation is characteristic for SLE B cells after stimulation

Ana-Luisa Stefanski[1,2], Annika Wiedemann[1], Karin Reiter[1], Andreia C. Lino[1], Thomas Dörner[1]

1Rheumatology and Clinical Immunology, Department of Medicine, Charité Universitätsmedizin Berlin and German Rheumatism Research Center Berlin (DRFZ), Berlin, Germany

2Department of Rheumatology, Immunology and Allergology, University Hospital of Bern, Switzerland

INTRODUCTION

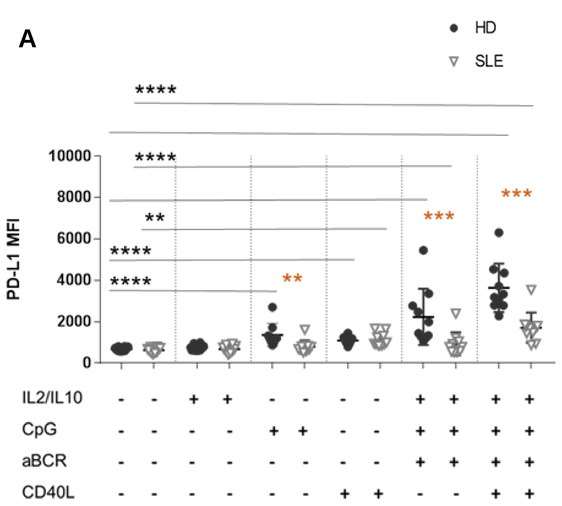
Programmed cell death 1 (PD-1) and its ligands PD-L1 and PD-L2 are known to play an important role in the inhibitory regulation between T and B cells during an inflammatory response [1]. Recent studies revealed that SLE patients present with anergic or post-activated B cells, characterized by hyporesponsiveness upon B cell receptor (BCR) and toll-like receptor (TLR)-9 stimulation as well as impaired T and B cell interaction [2]. The current study addressed the hypothesis that abnormalities of the PD-1 pathway might be involved in SLE B cells pathology and their post-activated status.

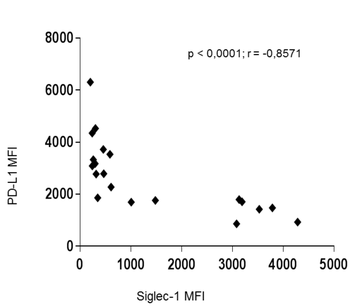
[1]Chamoto K, Al-Habsi M, Honjo T. Role of PD-1 in Immunity and Diseases. Curr Top Microbiol Immunol. 2017;

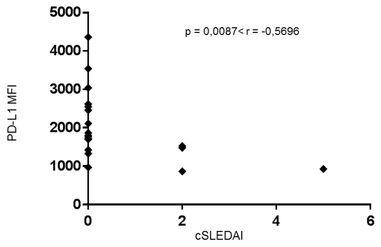
[2]Schrezenmeier E,, et al. Postactivated B cells in systemic lupus erythematosus: update on translational aspects and therapeutic considerations. Curr Opin Rheumatol. 2018.

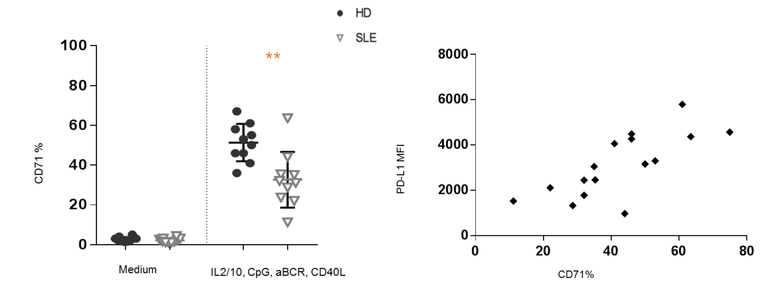
METHODS

PBMCs from SLE patients and healthy donors (HD) were stimulated with IL-2/IL-10, anti (α) - B cell receptor (BCR), CpG and CD40L alone or in combination. Expression of PD-1, PD-L1 and PD-L2 on CD19+CD20+ B as well as on CD3+ T cells were analyzed by FACS at baseline and after 48h of stimulation.







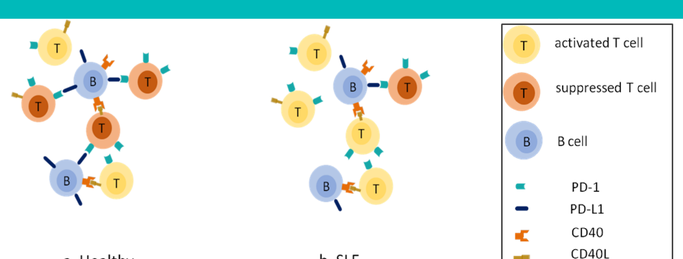


CONCLUSION

- **Post-activated lupus B cells present a phenotype of increased PD-1 and functionally diminished PD-L1 upregulation.**
- **The reduced PD-L1 expression upon B cell stimulation may result in an impaired inhibition of T cells in SLE, carrying a positive feed forward loop of lymphocyte activation.**

RESULTS

- Increased PD-1 expression was characteristic of unstimulated lupus T and B cells (not shown).
- After 48h stimulation with CpG alone and in combination, SLE B cells exhibited a substantially decreased upregulation of PD-L1 (p = 0,0006, Fig. A) compared with HD
- Diminished PD-L1 upregulation correlated inversely with the presence of interferon signature (measured by Siglec-1 expression; p < 0,0001, Fig.B) and the clinical SLEDAI (p = 0.0087, Fig. C).
- After 48h stimulation with α-BCR, CD40L and CpG, SLE B cells proliferated less then HD B cells (p = 0,0039. Upregulated PD-L1 expression correlated with proliferating B cells in SLE and HD (Fig D).



<u>Hypothesis upon diminished regulatory functions of SLE B cells</u>

- (a): activated HD B cells upregulate PD-L1 that suppress activated T cells via PD-1.
- (b): activated SLE B cells fail to upregulate PD-L1 leaving activated T cells unchecked.