Development of a Lymphoid Organ-Chip (LO Chip) to evaluate COVID vaccine boosting strategies

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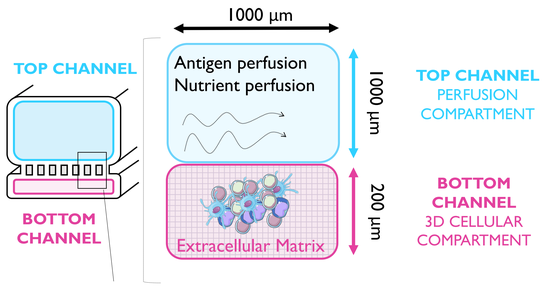
BACKGROUND

Secondary lymphoid organs provide the adequate microenvironment for the development of antigen (Ag)-specific immune responses. The tight collaboration between CD4+ T cells and B cells in germinal centers is crucial to shape B cell fate and optimize antibody maturation. Dissecting these immune interactions remains challenging in humans, and animal models do not always recapitulate human physiology. To address this issue, we developed an *in vitro* 3D model of a human lymphoid organ. The model relies on a microfluidic device, enabling primary human cells to self-organize in an extracellular matrix (ECM) under continuous fluid perfusion. We applied this Lymphoid Organ-Chip (LO Chip) system to the analysis of B cell recall responses to SARS-CoV-2 antigens.

METHODS

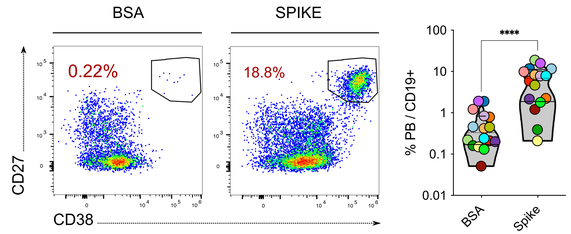
Emulate microfluidic S1® Chip



Microporous membrane

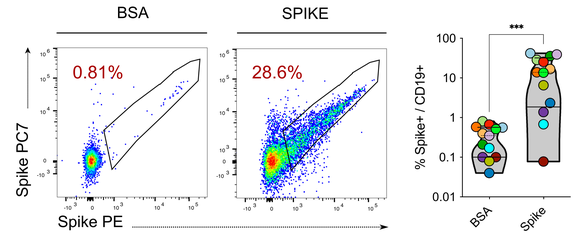
The LO Chip is based on the S1® microfluidic chip developed by Emulate: this chip composed of polydimethylsiloxane (PDMS) enables gaseous exchanges and fluid perfusion in its two compartments, to provide a long-term 3D culture system in near-physiological conditions. The top channel is perfused with antigen (Spike protein or SARS-CoV-2 mRNA vaccine), while the bottom channel contains PBMC seeded at high-density in a collagen-based ECM.

1- SPIKE PERFUSION INDUCES THE MATURATION OF B CELL INTO PLASMABLASTS



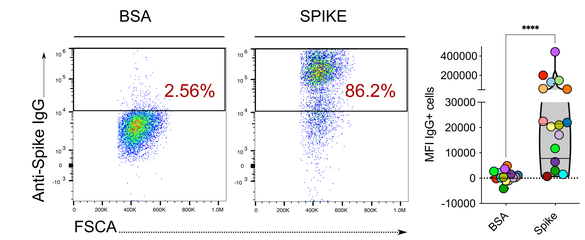
After 6 days of culture under BSA or Spike perfusion, PBMC from the bottom channel were harvested and analyzed by flow cytometry. Plasmablast are defined as CD38hi CD27hi cells among B cells; (n=16)

2- SPIKE PERFUSION INDUCES A MASSIVE AMPLIFICATION OF SPIKE-SPECIFIC B CELLS



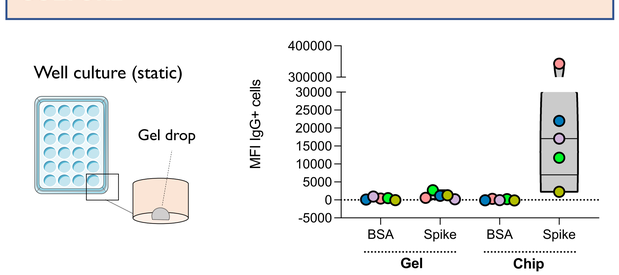
After 6 days of culture under BSA or Spike perfusion, Spike-specific B cell staining was performed using fluorescent Spike proteins labelled with two fluorophores (PC7 and PE); (n=13)

3- SPIKE PERFUSION INDUCES THE PRODUCTION OF SPIKE-SPECIFIC ANTIBODIES



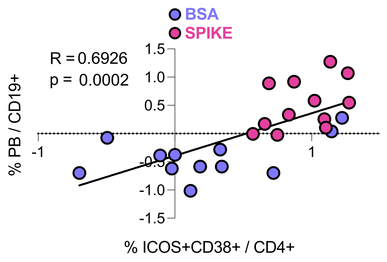
Spike-specific antibody production was investigated by S-flow assay, which is based on the exposure of Spike-expressing 293-T cells to chip effluent. Binding of spike-specific IgG is revealed by flow cytometry using a secondary anti- human IgG antibody; (n=16)

4- Ag-PERFUSION INDUCES HIGHER SPIKE-SPECIFIC ANTIBODY PRODUCTION COMPARED TO STATIC 3D CULTURE



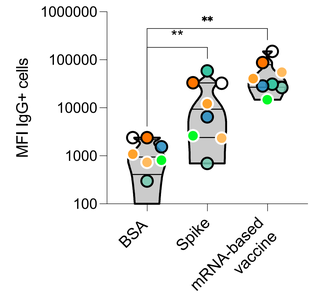
Production of Spike-specific antibodies was compared in static in-gel culture and LO Chips at day 6. PBMC were seeded at the same density and in the same volume of ECM gel in the two systems; (n=5)

5- CORRELATION BETWEEN THE PLASMABLAST RESPONSE AND THE CD4+ T CELL ACTIVATION LEVEL



CD4+ T cell activation was monitored after 6 days by measuring ICOS and CD38 co-expression and correlated to plasmablast maturation; (n=12)

6- COVID mRNA VACCINES INDUCES SPIKE-SPECIFIC B CELL RESPONSES IN THE LO CHIP



The COVID vaccine mRNA-based vaccine or the spike protein were perfused for 6 days in the top channel. Spike-specific antibody production was evaluated by the S-flow assay; (n=8)

CONCLUSIONS

- Early detection of memory B cell responses to the Spike antigen in the LO Chip (day 6).
- Higher memory B cell responses in perfused LO Chips than in static 3D cultures.
- Massive amplification of Ag-specific B cells upon Ag perfusion (*4x to 170x increase*).
- Versatile use of the LO Chip with different antigenic formulations: suitable for protein or mRNA-based vaccines evaluation.

THE LO CHIP PROVIDES A SCALABLE, AFFORDABLE, AND SENSITIVE PLATFORM TO STUDY MEMORY B CELL RESPONSES.

PERSPECTIVES

- Comparison of the memory B cell responses elicited by different boosting strategies (monovalent versus bivalent vaccines) in cohorts of patients vaccinated volunteers.

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