XI JORNADA DE JÓVENES INVESTIGADORES DEL I3A

Impact of tumour microenvironment stiffness on immune cell behaviour using Organ-on-chip models

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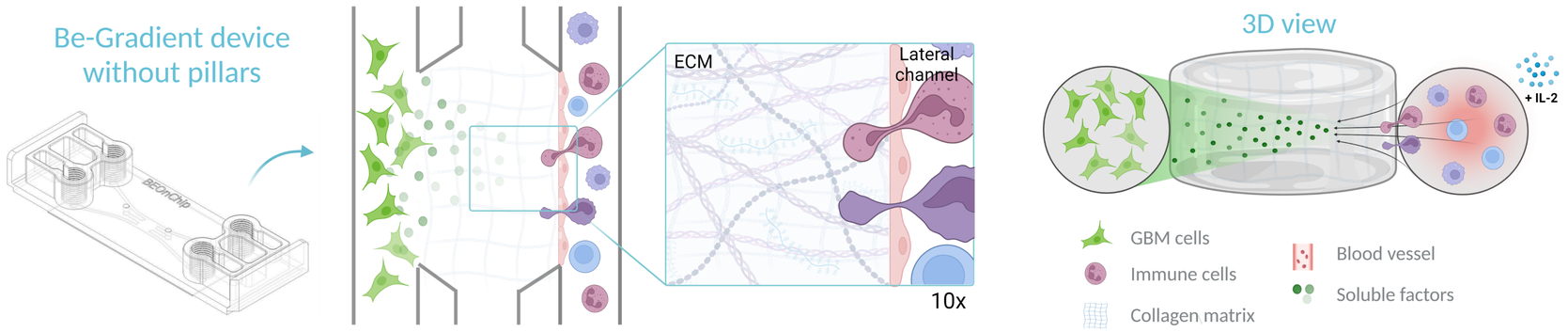
INTRODUCTION

The extracellular matrix (ECM) is one of the main factors that are modified by glioblastoma. The tumour is able to increase the stiffness of the ECM, hindering the infiltration of the immune system into the tumour and limiting the penetration of some chemotherapeutic agents into the tumoral mass. These mechanisms contribute to a suppression of immune surveillance and reduces the effectiveness of treatments, thus worsening the prognosis of patients. The recreation of this whole network is a difficult task to accomplish in conventional cellular models. Therefore, this study uses organ-on-chip devices to simulate the tumour microenvironment and study the effect of ECM stiffness on immune cell behaviour.

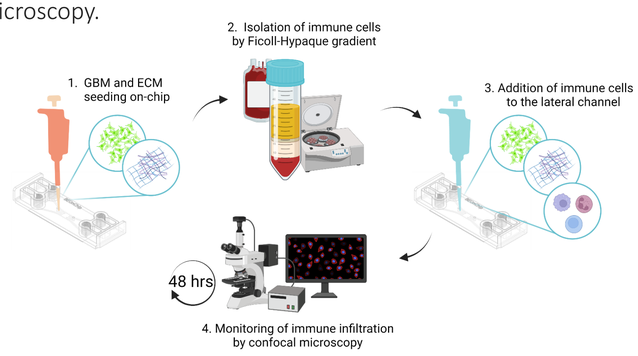
OUR APPROACH



Our approach consists of a microfluidic device containing two side channels separated by a central chamber where the extracellular matrix is incorporated. The major advantage is the absence of a physical barrier between the chamber and the channels, allowing direct interaction of the different cell types with the matrix. The central chamber contains the ECM, whose stiffness can be modified and therefore allows the study of different matrix environments. GBM cells are seeded in one of the side channels, from which they secrete a series of chemoattractants that produce a call effect and activate immune cells, located in the other side channel.

METHODS

1. 3D culture of the ECM matrix and GBM cells in the microdevice.
2. Extraction of PBMCs from blood donor samples.
3. Co-culture on-chip of GBM and immune cells in the lateral channel, separated by the ECM matrix.
4. Monitoring of immune cell infiltration in the ECM by confocal microscopy.



RESULTS

Effect of IL-2 on immune activation

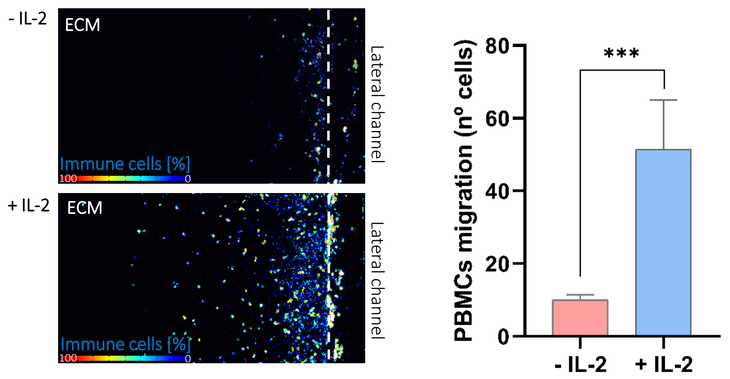


Fig. 1. Infiltration of immune cells in the ECM with and without the presence of IL-2.

✓ The addition of IL-2 significantly enhances immune activation and infiltration towards the tumour.

Presence of endothelium for immune attachment

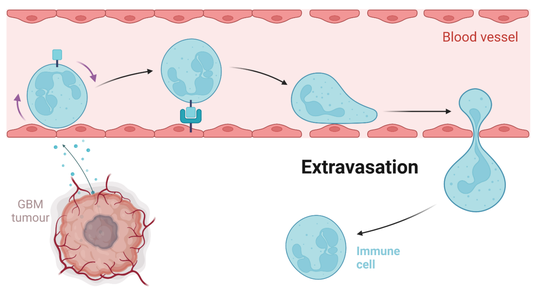


Fig. 2. Immune cell extravasation from the endothelium of a blood vessel into the target tissue.

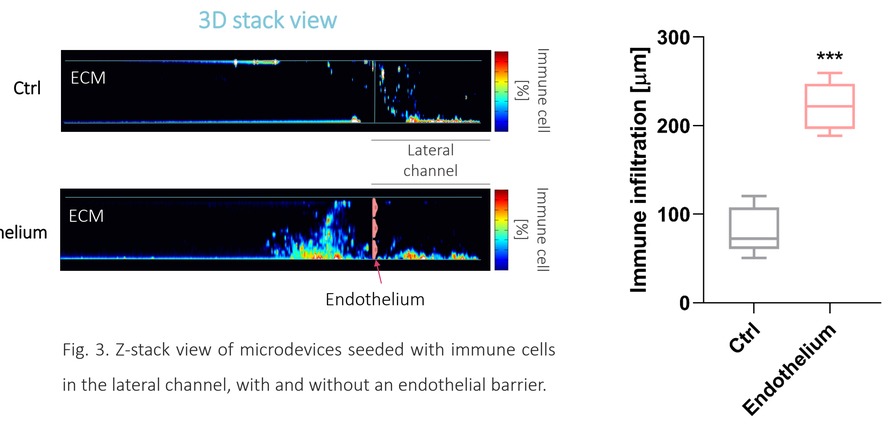


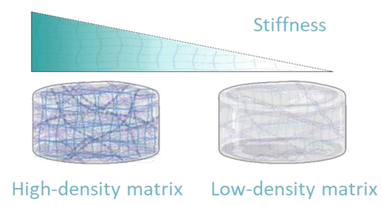
Fig. 3. Z-stack view of microdevices seeded with immune cells in the lateral channel, with and without an endothelial barrier.

Endothelium

✓ Immune cells rapidly infiltrated and invaded the low-density matrix, while they failed to enter any of the devices with a high-stiffness matrix, although the cells remained active.

Effect of ECM stiffness on immune infiltration

How does matrix stiffness influence the infiltration of immune cells?



✓ Immune cells rapidly infiltrated and invaded the low-density matrix, while they failed to enter any of the devices with a high-stiffness matrix, although the cells remained active. Controls did not induce infiltration, and even the absence of tumour stimuli resulted in cell death due to lack of activation.

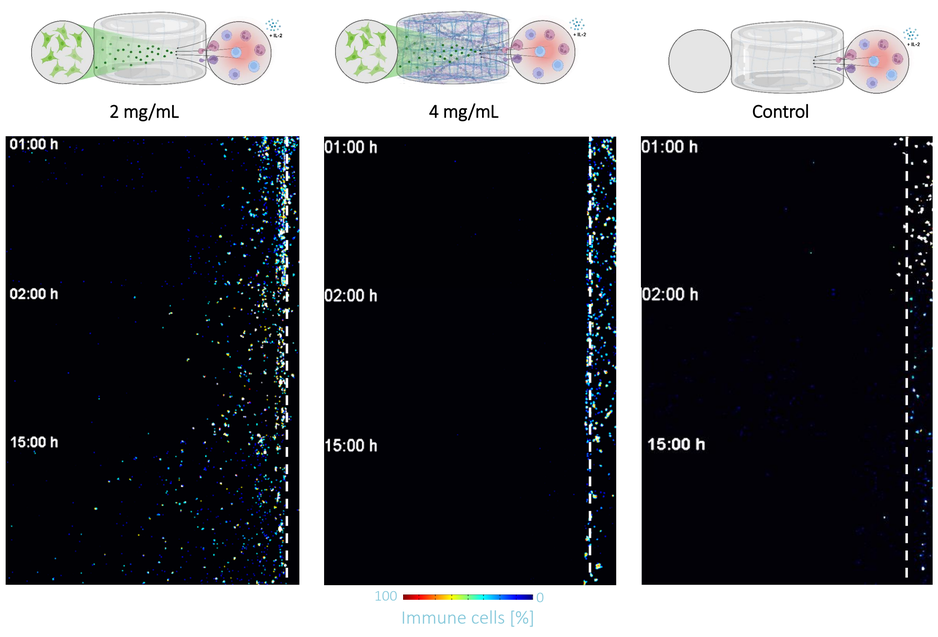
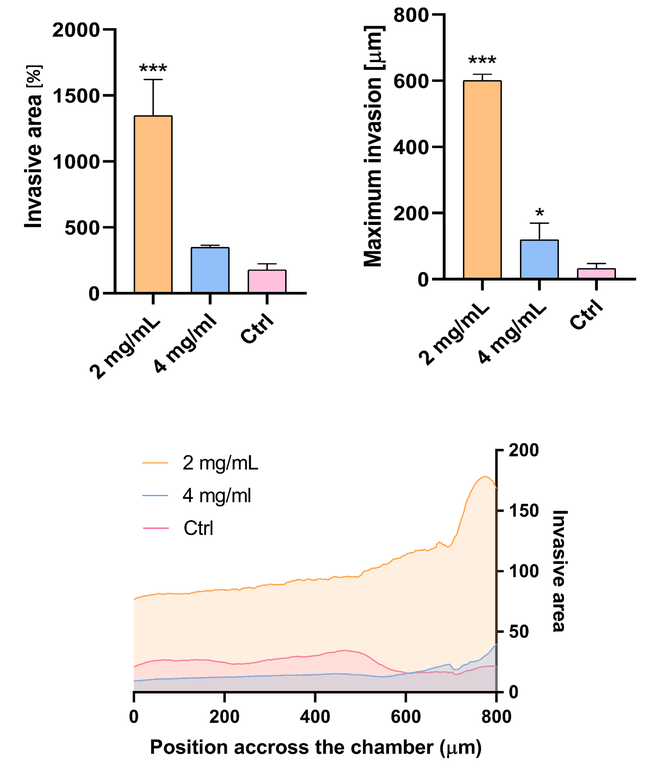


Fig. 4. Immune invasion in the ECM towards the tumour using different stiffness (2 mg/mL, 4 mg/mL). Control devices have not tumour cells in the other channel.



CONCLUSIONS

The extracellular matrix along with its stiffness modifications are capable of modulating the immune infiltration and its action against glioblastoma. The study of the tumour microenvironment, composed of tumour cells, immune cells and the extracellular component, is a very complicated task in conventional cell culture models.

In this study, we simulate the mechanobiological characteristics of the TME in organ-on-chip devices, as well as key mechanisms in the process of the immune response against the tumour. With this, we will be able to study the infiltration, proliferation, exhaustion and adhesion of immune cells, as well as their direct interaction with a complex ECM. A better understanding of mechanisms leading to immune suppression could help the development of more effective therapies in this aggressive tumour.

Would you like to see the invasion of immune cells in real time and even in 3D?

Scan the codes and you will have access to real chip videos!

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