Microfluidic tumor models help pre-clinical screening of T cell cancer immunotherapies

Cancer immunotherapy draws upon the patient's own immune system to recognize and fight the disease. One form of cancer immunotherapy is known as adoptive T cell therapy (ACT) consisting of isolation, genetic manipulation and reinfusion into the patient of engineered T cells capable of targeting tumour cells by antigen recognition. Although various methodologies have been clinically approved and have demonstrated some benefits for the treatment of liquid tumors (blood tumors) such as leukaemia and lymphoma, current effective therapies for solid tumors are very limited.

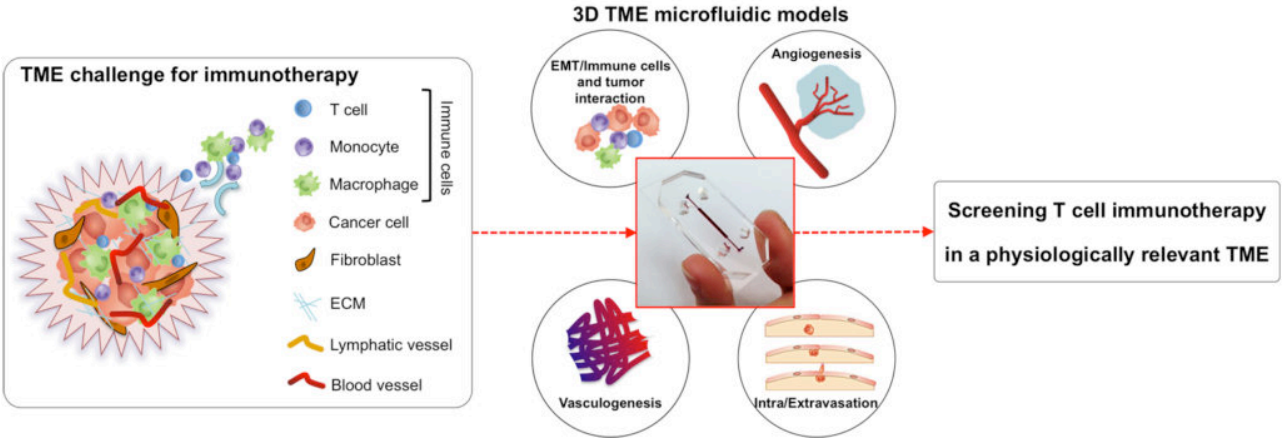

Fig. 1. Schematic representation of the tumour microenvironment (TME) and its main constituents that represent a challenge for T cell immunotherapy (left). 3D TME microfluidic models used to study cancer metastasis and tumor-immune system interaction mechanisms (center) represent a preclinical screening platform for T cell immunotherapies.

One of the main limitations for T cell immunotherapy against solid tumor is the tissue surrounding the tumor often referred to as the tumor microenvironment (TME). The TME is a complex system of immune cells, supporting cells, extracellular matrix (ECM), and lymph and blood vessels that restrain T cell interaction with the cancer cells (Fig. 1). In fact, once engineered T cells reach the tumour they need to both physically interact with cancer cells to destroy them and proliferate to maintain a high number of active T cells in the immediate vicinity of the tumor.

To mimic these interactions outside the human body (*in vitro)* and the characteristics of a three-dimensional (3D) TME we developed a microfluidic device that consists of microchannels imprinted in a transparent polymer called polydimethylsiloxane (PDMS) and closed by a glass coverslip. The microchannels are filled with liquids or hydrogels. Microfluidic platforms such as this allow (i) culture of multiple cell types together in a 3D ECM-like matrix; (ii) creation of gradients of different

compounds and molecules; (iii) visualization in real-time of cell interactions, migration and adhesion; and (iv) modulation of the microenvironment by varying the oxygen levels.

Importantly, specific mechanisms at each stage of metastasis, have been successfully modeled in these 3D microfluidic platforms (Fig. 1) to better recapitulate cancer progression and tumour-immune system interactions in the TME. Furthermore, the efficiency of engineered T cells has been tested in these 3D multicellular microfluidic devices to enable the screening of different engineering strategies with changes in biological factors or oxygen levels similar to those typically found in the TME.

As a result, 3D microfluidic tumour models represent a valuable assay for a fast and reproducible test of T cell strategies against solid tumours to fine-tune the therapy prior to application to the patient, thereby alleviating unwanted clinical side effects. Other synergistic combinations of T cells with radiotherapy or chemotherapy could be screened as well to identify the optimal response and to provide a rational and personalized therapy for cancer patients.

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