Personalized medicine in cancer treatment: preclinical evaluation of targeted therapies in innovative 3D tumor models

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Although the notable progress of the last years in early detection and antitumor efficacy obtained by combining new/approved drugs and/or targeted therapies with conventional treatments, i.e. chemo-and radiotherapy, metastatic and/or recurrent cancer types remain a major burden of disease worldwide. So, one of the greatest challenges in oncology is focused on setting up innovative personalized protocols able to overcome the individual variability in the response to cancer treatment and to counteract cancer cell plasticity and cancer stem cell proliferation, which are primarily responsible for the failure of conventional and precision therapies. In this context, we highlight the advantages and translational potentials in optimizing the growth conditions of3D spheroids-from different models of solid tumors -that, more likely than 2D cell cultures, recapitulate some tumor features, such as internal architecture, cellular heterogeneity, cell polarization, cell-to-extracellular matrix interactions, growth kinetics and diffusion of relevant soluble factors (oxygen, nutrient, cytokines, microRNAs), in order to more likely evaluate the ability of specific molecules, to inhibit disease progression and resistance to therapy. Ongoing studies are focused on tumor spheroids co-cultured with peripheral blood-derived immune cells, in both static and dynamic conditions, as valuable tools for testing how to enhance anticancer immunotherapy-based protocols. Recently, the integration of tissue engineering, material sciences, bioprinting and nanotechnology with molecular targeting and pharmacology has emerged as a promising strategy for setting up new and high-fidelity 3D preclinical models, such as cancer-on-a-chip microfluidics, bio-printed tumor constructs and organoids containing cell line-/patient-derived cancer cells, that have the ability to mimic several hallmarks of in vivo tumors to be used for high-throughput drug screening and tailored therapeutic approaches. The establishment of novel 3D *in vitro* systems in which tumor cells are deposited inside biopolymeric structures, such as silk fibroin scaffolds, recreates a more realistic cancer microenvironment useful for the identification of key molecules in solid tumor onset/progression that maybe clinically translated as biomarkers and molecular targets for a better management and outcome of cancer patients.