Cutting edge patient-specific “tumour-on-a-chip” technologies for personalised cancer treatments

Cancer is a complex and dynamic disease that is often very challenging to treat. Patients with the same cancer type often respond differently to the same chemotherapy regime, and oncologists don’t yet have the tools to predict the optimal treatment for each individual patient. However, with the latest advances in engineered tumour models, patient-specific or personalised cancer treatment is likely to become a reality. Dr Shay Soker and Dr Aleksandar Skardal at Wake Forest School of Medicine in North Carolina are combining their expertise in tissue model engineering and biofabrication technologies to develop a range of state-of-the-art tumour models from patient biopsies for use in personalised medicine to improve treatment outcomes.

Cancer is a complex and dynamic disease and determining the right course of treatment is often a major challenge. This is largely because patients with a given cancer type often respond differently to the same therapy due to genetic and phenotypic differences, and moreover, resistance to chemotherapy may arise during the course of treatment. Greater precision in cancer therapy calls for a way to predict the optimal treatment prior to administration. Advances in bioengineered patient-specific tumour organoids provide a highly attractive screening tool to pre-emptively identify the most appropriate treatment on an individual basis, providing empirical data with which to improve the overall success rates of cancer treatment.

WHAT ARE ORGANOIDS? Organoids are miniaturised cellular constructs, generated in the laboratory to serve as three-dimensional (3D) models of in vivo (real-life) tissues and organs. Although they are much smaller than their in vivo counterparts, they reflect many biochemical and physical aspects of an in vivo tissue. Since this field took off, organoid models have evolved significantly from simple cell spheroids (multicellular ball-shaped cell aggregates) to more complex 3D organ-on-a-chip systems. The earliest organoids were developed from easy-to-culture cell lines, but recent advances in 3D cell culture and biologically inspired biomaterials and biofabrication technologies have permitted the generation of organoids from freshly harvested human tumour-derived cells.

CLOSER TO REAL LIFE In contrast to conventional 2D cell culture in plastic vessels or culture media, the multicellular arrangements made possible by 3D culture technology permit interactions that normally take place in vivo, such as those that occur between cells, the molecules around them, and the extracellular matrix (ECM). Specifically, the 3D culture makes it possible to recapitulate physiologically relevant properties such as tissue stiffness, ECM topography (the shape and features of its surface), the presence and function of biological and biochemical factors such as growth factors and hormones, and modulation of tissue-tailored ECM to match the specific tissue type or organ of interest. External factors such as airflow, temperature fluctuations, fluid flow, and other physical forces can also be incorporated to better replicate physiologically relevant microenvironments.

CANCER ORGANOIDS Cancer organoids are typically developed using spheroids derived from cancer cells that are allowed to aggregate in specialised plastic tissue culture plates or hanging drop cultures. The use of specialised biofabrication techniques helps to ensure in vivo-like properties through the addition of physiologically relevant components to the 3D culture. This includes components that are normally found in the ECM, some of which are known to influence tumour progression, for example, collagen, hyaluronic acid, and laminin, to name a few. For further complexity and physiological similarity to cancer patients, multiple tissue and tumour organoids can be created and then combined in a single closed system. This facilitates the study of events that occur in two locations in the body, for example, metastasis, where a primary tumour spreads or metastasises to a nearby or distant tissue.

Dr Soker and Dr Skardal previously demonstrated success in generating liver-based organoids inoculated with colon cancer cells, in order to mimic in vivo metastasis from gut to liver. Detailed characterisation revealed morphological differences between the tumour organoids and 2D tissue culture models derived from the same cells, which may help to reveal clues about tumour cell growth in the body. Remarkably, manipulation of a known cancer pathway (the WNT pathway) in the tumour organoids altered their response to a widely used chemotherapy drug. Drs Soker and Skardal later developed a “metastasis-on-a-chip” system that allowed real-time tracking of fluorescently labelled colon cancer cells as they migrate from engineered gut tissue to downstream liver tissue within a circulatory fluidic device system that responds to environmental manipulation and drug treatment. These studies illustrate the enormous potential of tumour organoids to increase our understanding of tumour growth and metastasis, and for testing the response of tumour cells to current and newly discovered drugs.

ORGANOIDS IN PRECISION MEDICINE Precision or personalised cancer medicine exploits genetic sequencing technology to identify patient-specific tumour mutations and corollate them with available chemotherapeutic drugs. This differs from the conventional approach to therapy, whereby a treatment is administered based on its statistical likelihood of success in the broader population (as determined during clinical trials), and actual clinical benefit in a single patient is only known once treatment has occurred. Although great strides are being made in precision medicine, which also extends to diseases other than cancer, it is currently not standard practice to predict with certainty whether or not a patient will benefit from a specific cancer mutation, but it doesn’t allow an oncologist to investigate multiple candidate treatments in a safe and timely manner. Having a way to probe a patient’s tumour outside of their body would...

We anticipate patient-derived tumour organoid models being implemented in parallel with clinical practice.
permit the fast and parallel investigation of multiple candidate drugs to determine their effectiveness without potential danger in the form of detrimental side effects to the patient. On the other hand, tumour organoids prepared directly from patients’ tumour biopsies are fast becoming the most desirable way to probe tumours, and their development is now the main focus of Dr Soker and Dr Skardal’s research.

PATIENT-DERIVED ORGANOIDs

Earlier this year, Dr Skardal and collaborators successfully engineered 3D tumour organoids directly from fresh tumour biopsies in an attempt to create patient-specific models that can pre-emptively direct oncologists towards the optimal treatment. Here, tumour biopsies were surgically removed from two mesothelioma patients (mesothelioma occurs in the thin layer of tissue that covers the majority of our internal organs). These organoids mimicked the known tumour microenvironment and facilitated real-time testing of chemotherapy drugs. The team is now using advanced tissue culture technology to generate viable tumour constructs within a “tumour-on-a-chip” microfluidic device.

Importantly, because these organoids are human-derived, 3D, and replicate in vivo conditions, they represent human tumour physiology more accurately than other cancer models. The on-chip chemotherapy screening results mimicked those observed in patients themselves, suggesting the potential of such organoids for probing patient tumours. Importantly, the work also highlighted the benefit of mutation-specific drug testing; they confirmed the effectiveness of a chemotherapeutic compound against a particular mutation identified during the screen. This patient-derived tumour organoid strategy is adaptable to a wide variety of cancers and may provide the way forward in precision medicine oncology. Dr Soker is currently leading an NIH-funded project to investigate the potential of similarly bioengineered lung organoids to reveal clues about new mechanisms of lung tumour growth and invasion, with the ultimate goal to identify new therapeutic targets. Dr Soker and Dr Skardal have also been working on establishing tumour organoids from a range of other cancer types, including glioblastoma, colorectal cancer, appendiceal cancer, melanoma, sarcoma, multiple myeloma, and others.

STANDARDISATION REQUIRED

Despite the huge potential for tumour organoids in precision medicine, a number of challenges remain before they are likely to be approved by regulatory bodies. Firstly, the techniques used for the isolation and characterisation of tumour cells, organoid generation, drug screening and efficacy testing require standardisation. Although many of these techniques are currently used in research laboratories, they have yet to be used in FDA-regulated settings. Secondly, hospital staff and facilities will require training and adjustment to translate organoid technology from the laboratory to the clinic. Fortunately, a number of companies founded upon organoid and organ-on-a-chip technologies are already working with the FDA and other regulatory bodies around the world towards securing the necessary approval to incorporate these systems into their drug development pipelines.

A PROMISING FUTURE

Once 3D organoid technologies are standardised and regulated, they will be a gateway for personalised medicine applications to be more easily commercialised. Additional advances will further expand the capabilities of tumour organoid technology, potentially allowing for assessment of newer and highly complex therapies, such as immunotherapies, and the use of healthy tissue organoids to evaluate side effects of therapies under development. The use of bioengineered 3D tissue and tumour organoids is fast becoming the gold standard for organ and tissue replication ex vivo (outside of the body), and its applications extend also to the field of organ transplantation. In drug development and precision medicine, 3D culture systems are becoming the preferred way to recapitulate as many aspects of the corresponding in vivo tissue as possible. Indeed, studies conducted in recent years suggest that drug development has seen significant improvements in the diversity of assays available as a result of organoid systems and their in vivo like properties. Ultimately, if successfully deployed, tumour organoid technology has the potential to significantly drive advancements in oncology and change the way patients are treated.

Advanced methods in 3D culture technology allow us to work with designs and locations that were previously challenging to make possible.