EX VIVO MODELS TO EVALUATE IMMUNE-ONCOLOGY THERAPIES

The success rate of new therapies in the clinic is low as it is estimated that only 3.3% of cancer therapies were approved between 2000-2015[1]. One of the main reasons for failure of many anti-cancer therapies is inter- and intra-patient tumor heterogeneity in morphology, gene expression pattern, metastatic potential, and mutational and epigenetic profiles. To understand these heterogeneities and identify candidates that are likely to fail early, more physiologically relevant preclinical cancer models are needed. 3D cell culture models are increasingly being used to evaluate new anti-cancer therapies largely due to the availability of cancer cell lines, primary patient tumors and patient tumors xenografts.

Patient-derived xenografts (PDX) are some of the most well-established models that are developed by direct implantation and expansion of primary human tumor samples into immunocompromised mice. PDXs retained the tumor native architecture so successful PDX models provide physiologically relevant source material for cell-based assays. While data from PDX models have translational relevance, they have some challenges – generating PDX in immunocompromised mice is not guaranteed and the process is time consuming and expensive.

Patient-derived Explants (PDEs) are *ex vivo* models where fresh tumors from biopsies or surgical resections are directly used for drug studies PDEs are generated using little to no tissue disruption and include tumor cells, stroma, immune cells, and vasculature, so they are an accurate microcosm of the native tumor environment[2]. PDEs facilitate the interrogation of molecular and histological tumor characteristics in a single sample to construct a more complete picture of the tumor. However, PDEs can be extremely fragile and are liable to disintegrate rapidly and degrade over time so optimal culture conditions are necessary to obtain sufficient data. PDEs have several advantages and limitations compared to other 3D cell models. Since explants are generated from fresh tissue, they are more predictive of patient response, and the data generated from the explants can be correlated with the individual patient response. PDEs are a very useful model to study changes in immune cells in response to checkpoint inhibitors that are the primary drug targets for most tumor indications. PDEs have limitations primarily in terms of fresh tissue availability and the culture time frame. PDEs are not suited for longitudinal studies as they tend to start degrading in about 3 days, so there is a tight timeline to generate as much data as possible. Due to the short culture time, it is difficult to measure direct tumor killing effects of immunotherapies that can take several weeks to induce cytotoxicity. Despite these limitations, PDEs have a unique role in preclinical drug development of novel cancer therapies as they are the only model that truly represents the native tumor state.

Patient-derived organoids (PDOs) have become an established platform for preclinical validation of cancer drug assets. Primary tumor cell lines have been used to develop organoids that can be grown in a matrix that mimics the *in vivo* basement membrane. PDOs can be generated from small amount of patient tissues and can be grown and expanded to support drug screening and mechanism of action studies. Organoids cultured directly from patient samples can grow in days compared to PDX growth in animal models that can take several months. Additionally, PDOs are more efficient than PDXs in capturing the heterogeneity, polarity, cell-cell interactions, and structure of the native tumor[4]. However, PDOs have some limitations in that they do not fully recapitulate the tumor microenvironment and lack vasculature. To overcome those limitations primary tumor cells can be co-cultured with immune cells and cancer-associated fibroblasts[5]. Another limitation is that PDOs they may not represent the genetic heterogeneity of tumors, and it is possible that one clonal cell population that has a growth advantage will dominate the organoid. Despite limitations, PDOs are promising tools for disease modeling, gene therapy, understanding tumor growth and metastasis pathways, drug screening, and personalized and regenerative therapies, and evaluating the mechanism of action of single or combination therapies[6].

References:

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