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Commentary

Oncolytic virotherapy meets the human organoid technology for pancreatic cancers

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The history of oncolytic virotherapy (OV) begins more than a hundred years ago with the reports of spontaneous tumor remission and regression in coincidence with natural viral infections. Similar to that of other therapeutic approaches, the path of OV has been somewhat of a roller-coaster ride with initial enthusiasms rapidly followed by decline, and a recent resurgence of interest mostly due to technological advances in molecular biology [1]. Cancer models have had a significant role in shaping the evolution of the OV field, not only because they have enabled testing of oncolytic activity but also by permitting the elucidation of crucial aspects of virus biology, including mechanisms of pathogenicity and replication cycle. Therefore, technological advances in cancer modeling might further help pushing OV to the front lines of cancer treatment.

Several adaptive mechanisms limit the potential of oncolytic viruses as a standalone therapeutic approach for cancer. The true potential of OV probably lies in its combination with other treatment modalities (e.g., chemotherapy, immunotherapy) in order to increase anti-tumor responses in otherwise refractory diseases. Among the wide repertoire of viral species suitable for OV, oncolytic adenoviruses (OAs) are the most promising ones due to their potential of transducing both proliferating and quiescent cells and the capacity to carry large transgenes. Their direct oncolytic effect is just one of the advantages, as the release of cytokines and tumor antigens due to the lytic cell death might be able to modulate the tumor microenvironment in such a way to overcome the barriers that contribute to poor therapeutic responses [2].

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease due to late diagnosis and aggressive biological behavior. Surgical resection is the only curative approach, yet only a minority of patients present with a resectable disease at diagnosis. The dense desmoplastic reaction and the elevated intra-tumor heterogeneity dramatically hinder the path to the identification of effective treatment for PDAC. In the advanced setting, the standard treatment is based on chemotherapy regimens while immune-oncology approaches have demonstrated activity only in MSI (microsatellite instability)-high patients, which represent a rare PDAC population (around 1%) [3].

In this issue of *EBioMedicine*, Raimondi G et al. [4] showed that patient-derived organoids (PDOs), generated from normal and tumour pancreatic tissues, are suitable models to explore pre-clinical responses to OAs in PDAC. The pre-clinical evaluation of OAs' efficacy in human PDAC, as well as in other human solid tumors, has almost exclusively relied on monolayer cancer cell lines. Besides the incapacity to support the proliferation of non-transformed cells, monolayer cultures lack the three-dimensional tissue architecture and the physiologically relevant biomechanical properties, which ultimately affects virus internalization, intracellular trafficking, and dissemination [5]. Furthermore, the generation of monolayer cell cultures from PDAC specimens has been historically difficult and this has led to models that poorly reflect the original disease [6]. Since the development of the first protocol for growing three-dimensional organoids from mouse intestinal epithelium [7] to its later application to the human pancreas [8], the organoid technology has revolutionized cancer modeling and has shown that the PDOs platform might help overcome some of the intrinsic limitations of monolayer cell cultures, including predicting the impact of interpatient diversity on treatment efficacy [6].

In their study, Raimondi and colleagues [4] first tested the replication capacity of the oncolytic adenovirus in organoids derived from normal pancreatic tissues. While acknowledging the fact that normal pancreatic organoids are exclusively composed of ductal (or ductal-like) cells, the authors demonstrated quite convincingly that the virus failed to replicate in non-transformed proliferative cells, thus suggesting that this platform might be used to test oncoselectivity. The possibility of testing activity of therapeutic agents, including viruses, in non-transformed proliferative cells represent a major advantage of the organoid culture system. This is particularly relevant for virotherapy, as biosafety is obviously a great concern and dictates the delivery method. In this scenario, a library of organoids derived from different specialized tissues might help addressing virus oncoselectivity.

Large interpatient variability is observed for virtually all available therapeutic agents in pancreatic cancer; therefore, being able to

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model responses at an individual level might help improving the clinical management for this disease. Although other groups already proved the predictive ability of PDOs to identify responders to chemotherapeutic agents [6] in PDAC, this is the first study showing that PDAC organoids represent a reliable platform to test patient-specific response to OV as single agents or in combination. Indeed, the authors showed that tumoral PDOs exhibited heterogenous responses to oncoviruses *in vitro*, and this was predictive of antitumor efficacy *in vivo* [4]. Moreover, they proved the feasibility of the platform to test oncolytic virotherapy and chemotherapeutic combinatory treatments. They also demonstrated that oncolytic viruses have a comparable efficacy on organoids established from primary tumor and distant metastasis, regardless of the increased genetic instability of the latter. However, since cancers are complex ecosystems and pancreatic organoids are only composed of one cell type, we envision the refinement of organoid platforms to include key components of the tumor microenvironment (immune and stromal cells) for proper biological and preclinical assessment of oncolytic virotherapy. Few experiences already exist of organotypic platforms that enable either short-term preservation of the native microenvironmental components [9] or refinement of culture conditions to accommodate the growth of stromal cells [10].

In conclusion, increasing evidences are suggesting the possibility of organoid-based personalized medicine, and this work gives an important contribution to the field by proving the feasibility of PDOs platform for evaluating selectivity and efficacy of OA's at individual patient level.

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