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Spotlight

Organoids as a tool in drug discovery and patient-specific therapy for head and neck cancer

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Organoids more accurately reflect tumor microenvironment than traditional models. Millen et al. demonstrated organoids replicated from patient tissues may predict patient-specific response to radiation therapy and have potential to be utilized for validation of biomarkers in drug discovery and treatment planning.

Despite advances in surgical techniques, modifications to radiation therapy, and new drug approvals, the 5-year overall survival rate for human papillomavirus (HPV)-negative head and neck cancers (HNCs) has remained stagnant at approximately 55% over the past three decades.[1] Traditional *in vitro* research in HNCs has relied on two-dimensional (2D) cell layers that poorly reflect the *in vivo* tumor microenvironment. Recently, 3D tumor organoids have revolutionized the ability to more closely model the tumor microenvironment, and they are a promising model for HNCs. Despite their potential advantages for research in HNCs, their utilization remains low relative to other solid tumors (including lung, prostate, and pancreas). In fact, over the past 5 years, fewer than 5% of studies in HNC drug discovery incorporated use of 3D *in vitro* models.[2]

One potential reason is that the rate of establishment and re-expansion from tumor samples has proven challenging in HNCs relative to other tumor types.[2] In the present study, Millen et al. have shown a high success rate for HNC organoids, successfully establishing the largest HNC biobank to date including more than 100 organoids, each derived from a unique patient.[3] They report reliable recovery and expansion of 71% after cryopreservation, which is on par with many other solid tumors. In addition, they have developed organoid models of two rare HNCs not previously described, as well as four salivary gland subtypes of HNCs that were shown to retain the characteristics of native salivary tissue (through immunohistochemical staining), adding to previous salivary tumor work by Wang et al.[4] This further supports the ability to derive organoids from a wide variety of tissues and provides a foundation for establishing additional head and neck tumor organoids outside of traditional squamous cell cancers, with the potential to represent a wide array of HNC types.

This expanded biobank and validated processes for HNC organoid development may aid in establishing reliable biomarkers to guide HNC treatment. A unique challenge in treating HNCs is *the unpredictable response to adjuvant therapy*. Currently, the only agent requiring a diagnostic biomarker is pembrolizumab (PD-L1) despite the targeted nature of many HNC drugs. For example, epidermal growth factor receptor (EGFR) expression is not a reliable biomarker and is poorly predictive of therapeutic response to the EGFR inhibitor cetuximab. Tanaka et al. proposed the utilization of HNC organoids for biomarker discovery and patient treatment stratification based on their ability to create the first head and neck squamous cell carcinoma organoid line that accurately reflected the native patient tumor and displayed similar response to cisplatin and docetaxel in both *in vitro* and *in vivo* models.[5] Here, Millen et al. tested the utility of biomarker development by comparing 6 different drugs targeting specific molecular pathways (e.g., PIK3CA) in 31 organoids. The responses between donors had high variability even when known targetable mutations were present. Similarly, a PRMT5 inhibitor demonstrated differential response except in CDKN2A null models, where increased sensitivity to PRMT5 inhibitors was shown. These findings highlight the potential of using organoid cohorts to identify likely responders to specific agents with greater fidelity than using tumor mutational profiles. Ultimately, further predictive clinical validation between organoid and patient responses to therapies will be of high interest in advancing precise and effective treatment options for patients.

Beyond biomarkers, Millen et al. compared organoids from 15 patients undergoing adjuvant radiotherapy (RT) and showed a statistically significant correlation between radiosensitive organoids and longer relapse-free survival time. This correlation was not demonstrated in organoids from 6 patients who underwent primary RT. While the data presented here suggest the organoid response to radiation correlates well with patient-specific response, Millen et al. reported no clear correlation between organoid and patient-specific response to chemoRT. It is possible the lack of correlation is secondary to insufficient power with a limited sample. Additionally, there may be limitations in current organoid models to capture the full microenvironment in patients. The organoid models developed by Millen et al. showed higher copy-number variations than tumor tissue from which they were derived, which is expected given that the organoids are comprised predominantly of tumor cells. This highlights an important future direction in HNC organoid research. The absence of the supporting stromal tissue and immune cell populations may limit the ability to assess the full effects of RT. Organoids

integrating heterogeneous cell populations including immune cells have been developed in other solid tumor models.[6,7] These would be of similar value in HNCs to better reflect the true tumor microenvironment to more accurately model response to RT for personalized patient-directed therapies.

In summary, Millen et al. have developed a robust biobank of patient-derived HNC organoids that can be reliably recovered, expanded, and that includes less common variants of HNCs. These organoids accurately reflect the tumor from which they were derived, and, in the case of adjuvant RT, treatment response correlates well between patient and organoid. Taken together, the authors present compelling data in support of using HNC organoids for identification of biomarkers for drug screening, as well as screening for patient-specific therapy.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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