UNCOVERING THERAPEUTIC VULNERABILITIES IN GASTRIC CANCER WITH PATIENT-SPECIFIC MICROPHYSIOLOGICAL TUMOR SPHEROID SYSTEMS

Background In recent years, microfluidics-based microphysiological systems (MPS) have emerged as promising tools for reproducing the structural and functional characteristics of human organs in vitro, including the tumor microenvironment (TME). These platforms integrate key components of tumors, such as blood vessels, tumor cells, and immune cells, and allow for ex vivo replication of organ-level pathophysiology. Moreover, patient-specific MPS reconstructed from patient specimens can be a tool not only for the investigation of patient lesions, but also for the formulation of personalized anti-cancer treatment strategies.

Methods We developed a patient-specific MPS that allows tumor spheroids to co-culture with blood vessels and provides microenvironmental factors. And, we generated patient-derived tumor spheroids using 26 primary tumor tissues and 19 malignant ascitic fluid samples from patients with gastric cancer (GC). The tumor spheroids were then co-cultured in three dimensions with human umbilical vein endothelial cells in the system to form a model of tumor angiogenesis. The models were cultured for 6 days with intermittent drug treatments. Extensive characterization of the angiogenesis model was conducted using RNA analysis, protein analysis, and confocal microscopy (figure 1a).

Results We successfully replicated the TME, specifically tumor angiogenesis, using patient samples implanted on the TumorSpheroChip. By assessing morphological characteristics of blood vessels and tumors, we accurately measured tumor angiogenesis expression in individual patients. This analysis revealed a significant correlation with the angiogenesis signature obtained from sequencing data (figure 1b). To explore treatment options, we identified GC patients with high angiogenesis signature expression and tailored combination therapy based on their genetic variants. In patients with MET overexpression, we conducted a combination therapy study utilizing Savolitinib and Ramucirumab, an anti-angiogenic drug. No significant difference in vessel density change was observed with small molecule monotherapy. However, treatment with ramucirumab demonstrated a significant reduction in bud length change compared to savolitinib (p = 0.0167). Moreover, combination therapy also exhibited a significant reduction in bud length change compared to savolitinib (p = 0.0211).

Conclusions Through the integration of multi-modal data, including microfluidic functional assays and genomic profiling, we made a significant breakthrough. This approach unveiled consistent patterns of tumor angiogenesis in 45 GC patients, utilizing data from genetic profiling and the TumorSpheroChip. Our research not only identified novel indicators for GC diagnosis but also devised strategies to explore tailored anticancer therapies for individual patients. This innovative preclinical drug testing platform holds immense potential for guiding precision medicine on a larger scale, specifically in the context of patient-specific TME and immunological studies.

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Ethics Approval This study was conducted in strict adherence to ethical guidelines, with all participating patients providing their informed consent through an approved Institutional Review Board (IRB) consent form (IRB#2021–09-052) at Samsung Medical Center (SMC). The research adhered to the principles outlined in the Helsinki Declaration and the Guidelines for Good Clinical Practice. A total of 45 samples were collected from patients with advanced gastric cancer (GC), comprising 26 primary tumor samples obtained from surgical procedures and biopsies, and 19 samples collected from peritoneal dialysis fluid. Additionally, this study is registered on ClinicalTrials.gov under the identifier NCT02589496.

Consent We appreciate your understanding and cooperation in maintaining the confidentiality of our research until it is officially published. Thank you for your attention to this matter.