Editorial Commentary

Conditional reprogramming technology: a new tool for personalized medicine in bladder cancer?

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Urinary bladder cancer is a heterogeneous group of tumors comprising various histological or molecular subgroups (1). Although cisplatin-based combination chemotherapy remains the standard of care in patients with advanced disease, many of them either have no clinical benefit from or are ineligible for systemic chemotherapy (2). More recently, systemic immunotherapy against bladder cancer, including programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade, has become available (3). With such therapeutic advances, however, the prognosis for advanced bladder cancer has not been significantly improved during the past several decades.

The development of targeted therapy represents an exciting new option for the treatment of bladder cancer. Several approaches have then emerged in an attempt to personalize systemic therapy and include the use of genomic profile data derived from the patient's tumor. Patient-derived xenograft models have provided such a promising approach which enables to reflect biological and molecular characteristics of individual tumors (4). Indeed, a variety of patient-derived xenograft models for bladder cancer have been applied to predict sensitivity to anti-cancer agents (5). However, the limitations of these models that need to be overcome include high cost, as well as long latency time of initial engraftment and passages, uncertainty to maintain tumor characteristics over passages, artificial tumor microenvironment (as a subcutaneous model), and requirement for immunocompromised hosts.

Conditional reprogramming established as *in vitro* primary epithelial cell cultures involves co-culture of feeder cells with human biospecimens in the presence of a Rho kinase inhibitor (6). This approach has been used to rapidly generate patient-derived cultures from several malignancies, such as prostate and breast cancers (6-8), while a failure in establishing primary and metastatic lung cancer cell cultures has been documented (9). To the best of my knowledge, its application to urothelial cancer has never been reported.

The recent pilot study by Kettunen *et al.* (10) aimed to explore the feasibility of the conditional reprogramming technique for generating patient-derived bladder cancer cell cultures and subsequent screening for drug sensitivity. Of six conditional reprogramming cultures from fresh bladder tumor specimens obtained by transurethral resection or radical cystectomy [i.e., 4 cases of high-grade urothelial carcinomas (pTaN0, pT1N0 ×2, pT4aN1), a case of pT4aN1 small cell carcinoma, a case of pT2bN0 adenocarcinoma], four (67%; 3 urothelial carcinomas and a small cell carcinoma) were successfully established (i.e., cultured for 5 passages) and re-propagated after cryopreservation for further analysis. Although all these four cultures exhibited similar morphology to that of the corresponding tumors, exosome sequencing revealed that only two of them retained the majority of genetic alterations, including *RB1* mutation, detected in respective parental tumors (pT1 urothelial carcinoma and small cell carcinoma). In immunohistochemical staining in these two cases, original tumors and their derived cultures shared an identical immunoprofile, except the emergence of strong cytokeratin-5/6 expression in the urothelial carcinoma culture, indicating a shift towards a basaloid phenotype.

In the remaining two cultures that did not retain the specific driver mutations, overgrowth of contaminated non-malignant cells was thus suggested. Drug sensitivity screening test in the two conditional reprogramming cultures (i.e., pT1 urothelial carcinoma and small cell carcinoma) further demonstrated that both were sensitive to conventional agents, such as cisplatin, gemcitabine, and taxanes, as well as inhibitors of proteasome and topoisomerase. The small cell carcinoma culture was also found to be sensitive to statins. Unfortunately, the authors did not correlate between the findings in the sensitivity screening assay and treatment data in these patients.

As aforementioned and being used for anti-microbial susceptibility testing for many years, multiple approaches have been described in an attempt to screen individualized drug sensitivity in oncology patients. Nonetheless, laboratory-based commercial assays for which current evidence supports their use in oncology practice remain unavailable (11), presumably due to much higher complexity in tumor genomes and heterogeneity in tumor clones, compared with those in microorganisms. Further studies are thus required to develop such tests that must not only yield high reproducibility and useful information which aids in drug selection, without being affected by tumor heterogeneity, but also be cost-effective and time-efficient.

Does the approach described by Kettunen *et al.* (10) have a potential for being an assay which satisfies the above requirements? It can be said that this is somewhat better than traditional approaches, such as patient-derived xenograft models, to establishing patient-derived bladder cancer cells for more proficient drug sensitivity screening. Otherwise, it is difficult to state if this new approach represents an assay which reliably informs choice of anti-cancer drugs in individual patients with bladder cancer, especially due to the relatively low success rate [33% (2 of 6 cases)] and the lack of definite clinical correlations reported in the article. Nevertheless, it would be a pilot study that clearly indicated the feasibility of application of conditional reprogramming technique to personalized drug sensitivity screening for bladder cancer. In a more recent study, conditionally reprogrammed bladder cancer cells derived from urine samples were assessed for drug responses (12). The overall success rate of urine conditional reprogramming cultures was relatively high [50 (83.3%) of 60 cases, including 41 (85.4%) of 48 high-grade tumors and 9 (75.0%) of 12 low-grade tumors], along with 79.7–82.6% of genetic variation profile shared with the parental tumors. Drug sensitivity tests in 13 cases showed both similar and dissimilar responses to some conventional agents, including cisplatin, gemcitabine, epirubicin, and pirarubicin, in select patients, whereas no clinical susceptibility information for other specific drugs that considerably inhibited the growth of urine cultures, such as afatinib, lapatinib, paclitaxel, docetaxel, and bortezomib, was provided.

In summary, a new and exciting technology which offers the possibility to rapidly generating patient-derived bladder cancer cells in culture has recently been adapted. This approach appears to be suitable for large-scale screening testing for oncology drugs. However, the success rate of conditional reprogramming cultures remains not high, and substantial clinical outcome correlation data are not available. In addition, the tumor microenvironment, which is not typically replicated in *in vivo* culture systems yet is often critical for determining drug sensitivity, may need to be simulated in combination with conditional reprogramming cultures via, for example, three-dimensional culture models.

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Footnote

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