Personalized Chemotherapy Profiling Using Cancer Cell Lines from Selectable Mice

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Abstract

Purpose: High-throughput chemosensitivity testing of low-passage cancer cell lines can be used to prioritize agents for personalized chemotherapy. However, generating cell lines from primary cancers is difficult because contaminating stromal cells overgrow the malignant cells.

Experimental Design: We produced a series of hypoxanthine phosphoribosyl transferase (hprt)-null immunodeficient mice. During growth of human cancers in these mice, hprt-null murine stromal cells replace their human counterparts.

Results: Pancreatic and ovarian cancers explanted from these mice were grown in selection media to produce pure human cancer cell lines. We screened one cell line with a 3,131-drug panel and identified 77 U.S. Food and Drug Administration (FDA)–approved drugs with activity, and two novel drugs to which xenografts of this carcinoma were selectively responsive to both drugs.

Conclusion: Chemotherapy can be personalized using patient-specific cell lines derived in biochemically selectable mice. Clin Cancer Res; 19(5); 1139–46. ©2012 AACR.

Introduction

Selecting the most appropriate chemotherapy for a given patient has historically been based on histopathology and past studies showing that specific drugs are generally active against that malignancy. However, drugs deemed active against a particular type of cancer are most commonly active in only a subset of patients with those cancers. Furthermore, chemotherapeutic agents are generally more toxic and expensive than most other medications in widespread use. Accordingly, an alternative strategy is to test functionally whether a given patient’s cancer is likely or not to respond to specific drugs. In vitro chemotherapy sensitivity and resistance assays (CSRA), a natural extrapolation of antimicrobial susceptibility testing, was first reported in 1957 (1). Some 50 years later, however, the official position of the American Society of Clinical Oncology has been that this type of testing is still not ready for routine clinical use (2). Problems with CSRA include the many different formats for this testing (2), and results from clinical trials, comparing CSRA-guided therapy with conventional treatment, have varied from no significant difference to highly significant benefit (3). Finally, most groups test cancer cells immediately after resection, and these may be sick or dying from hypoxia, anesthetic drugs, or overnight shipping and so any toxicity to these cells may reflect synergistic toxicity of the drugs tested with any of these effects.

We hypothesize that low-passage cell lines might better represent their respective tumors and therefore more accurately predict in vivo chemosensitivity. Isolating cancer cell lines, however, can, counterintuitively, be difficult, especially from solid primary tumors (4). To date, the success rate for the generation of cell lines is only 10% to 40% for many solid tumors (4–8). The most significant barrier to routine cancer cell line production is that when tumors are explanted into tissue culture, fibroblasts and other stromal cells proliferate, overgrow, and eliminate the malignant cells.

We report production of nude-, severe combined immunodeficiency- (SCID), and NSG- [Nonobese diabetic (NOD), SCID, interleukin-2 receptor gamma (IL2Ry)] hprt-null mice. During growth of implanted human cancers in...
Translational Relevance

Clinical cancer lines are essential for functional studies of cancer. When explanted tumors are grown in vitro, however, noncancer fibroblasts paradoxically overgrow the malignant cells. Here, we report production of a series of immunodeficient hypoxanthine phosphoribosyl transferase (hprt)-null mice. When human tumors are expanded in these mice, the resultant tumor is composed of human cancer cells and biochemically defective mouse stromal cells. When these tumors are explanted into culture and grown in hypoxanthine–aminopterin–thymidine (HAT) media, human cancer cell lines can be readily isolated. We show proof-of-principle of the mice for personalized cell line isolation and chemosensitivity testing. This approach may be used to guide chemotherapy selection in the future.

these mice, biochemically defective mouse stromal cells replace the human stromal cells from the original tumor (9, 10). After explanting these xenografts into culture, mouse cells can be eliminated by selection in hypoxanthine, aminopterin, and thymidine (HAT) media (11, 12) to isolate pure human cancer cells. Using this system, we isolated a total of 6 pancreatic ductal adenocarcinoma (PDA) cell lines and 1 ovarian cancer cell line. One of the PDA cell lines was isolated from the corresponding surgically resected sample and tested for in vitro chemosensitivity using a 3,131-drug panel (13). In comparison to other PDA cell lines, this cell line in vitro was differentially more sensitive to digitoxin and nogalamycin, which correlated with in vivo response in mice, where the same 2 drugs showed selective activity against xenografted tumors. These data suggest a possible novel paradigm for functional personalized chemotherapeutic selection by isolating low-passage cancer cell lines and screening them with large drug panels.

Materials and Methods

Patient samples and xenografting

Primary tumors from patient-derived resection specimens or xenografts from standard nude mice were harvested with informed consent and Institutional Review Board (IRB) approval. They were implanted in anesthetized standard B6 nude and hprt-null B6 nude mice. Following a small skin incision, a 5-mm sample coated with Matrigel Matrix (BD Biosciences) was implanted subcutaneously in each upper flank. The incision was closed using staples, and the site was disinfected with Betadine (Purdue Frederick). Among the 6 pancreatic cancers, 3 were selected because they were familial and 3 because they have undergone full exomic DNA sequencing as xenografted samples (14).

Tumor harvest and culture

When tumors reached approximately 1 cm in diameter, mice were sacrificed and tumors harvested. In a laminar flow biosafety cabinet, tumors were finely minced and incubated in Dulbecco’s Modified Eagles’ Media (DMEM) containing 750 U/mL of type IV collagenase (Invitrogen) and 500 U/mL of hyaluronidase (Sigma-Aldrich Inc.) for 1 hour at 37°C and pipetting up and down 20 times to mechanically fragment the tumor. The cell solution was plated at 0.5, 1, and 2 mL per well on 6-well plates coated with or without type I rat tail collagen (BD Biosciences) in minimum essential media (MEM) with 20% FBS, supplemented with standard concentrations of penicillin/streptomycin, 1-glutamine, 5 mg/mL of human recombinant EGF (all Invitrogen), and 0.2 U/mL of human insulin (Sigma-Aldrich). Following 2 days of recovery (designated day 0), 1× HAT (100 μmol/L sodium hypoxanthine, 400 nmol/L aminopterin, 16 nmol/L thymidine; Invitrogen) media were fed to half of the cultures. Cells are fed with or without HAT media every 2 to 3 days. All cell lines were confirmed as patient in origin by DNA fingerprinting with the Powerplex 1.2 Kit per manufacturers’ instructions (Promega). They were also stained with anti-cytokeratin (Ventana, 760-2595) and anti-smooth muscle actin (Ventana, 760-2835) by immunohistochemistry and shown to be tumorigenic in nude mice.

Chemosensitivity testing—initial library screening and confirmation

Cancer cells were screened for chemosensitivity using the Johns Hopkins Drug Library (JHDL) consisting of 3,131 drugs arrayed in 96-well plates. This includes 1,907 U.S. Food and Drug Administration (FDA)-approved drugs, 570 drugs approved in other countries, and 654 other drugs in various phases of development (13). All drugs are maintained at −70°C at a stock concentration of 200 μmol/L in PBS containing 2% dimethyl sulfoxide (DMSO) and 10% FBS.

Tumor cells were subcultured, counted, and inoculated into 96-well plates at 5,000 cells per well in complete media and allowed to adhere overnight. Drugs were then added to the plates in duplicate wells at a final concentration of 10 μmol/L for a total of 48 hours. After the first 24 hours in drug, 1 μCi [3H]-thymidine was added and incubated for an additional 24 hours (in both drug and [3H]-thymidine). Cells were then trypsinized using 1× trypsin-EDTA (Invitrogen). The suspended cells were transferred onto Filter-Mat A glass fiber filters (Wallac) using the Harvester-96 cell harvester (Tomtec). The glass fiber filters were washed 5 times with water to wash away unincorporated free [3H]-thymidine. On each plate, the first and last columns were used as no-drug controls. Incorporated thymidine was read on a MicroBeta plate reader (Perkin Elmer), and the mean percentage of inhibition was calculated relative to no-drug control wells. A histogram of the percentage of inhibition for the drugs in the JHDL was established using 2.5% size bins, and normal distribution curve fitting was conducted by the least-squares method using GraphPad ver. 5.02 (GraphPad Software Inc.). The mean ± 3 SD encompasses 3,014 drugs. Using Gaussian statistics and 3 SD as the cutoff (40.4% inhibition), then we expect about 4 drugs to be...
false-positives among the drugs showing 40% to 100% inhibition (2,817 × 0.0013 = 3.7).

IC₅₀ values of selected drugs were determined from percentage of growth inhibition of 10 different concentrations of the drugs obtained in the same experimental design described above. IC₅₀ values of each drug for each cell line were calculated using 4-parameter logistic equation with 3 replicates results by GraphPad ver. 5.02.

Growth inhibition of subcutaneous xenografted tumors

Tumor xenografts were generated by subcutaneous injection of 10 × 10⁶ cells bilaterally into 6-week athymic nude-Foxn1⁰⁻¹⁰ mice (Harlan). Tumor volumes were measured, and when the tumors reached approximately 100 mm³ in size, the mice were stratified (day 0) to treatment and nontreatment groups with 5 mice per group so that each group was equivalent based on tumor volume. Tumor volume is obtained by the formula: length × (width)² × 0.5, where length is the longest diameter and width is the shortest diameter perpendicular to the length. The mice received treatment with daily intraperitoneal injection of nogalamycin (0.2 and 1 mg/kg in vehicle), digitoxin (0.4 and 2 mg/kg in vehicle), or vehicle (0.9% NaCl with 1% DMSO) control for 30 days (days 1–30). Tumor volumes were measured twice a week. At the completion of the study, the mice were euthanized and tumors were measured, harvested, and weighed. The tumor volume index (TVI) was determined by dividing the treatment values by the control group for each cell line (I.e., the mean tumor weight of control group for each cell line is 100). Statistical analysis was conducted using the unpaired Student t test on Graph Pad Prism ver. 5.02.

Results

Production of hprt-null immunodeficient mice

A series of hprt-null immunodeficient mice, including nude hprt-null (Supplementary Fig. S1), SCID hprt-null (Supplementary Fig. S2), and NSG hprt-null, were produced by breeding immunocompetent hprt-null mice with the appropriate immunodeficient mice (see Supplementary Information). Mice that are homozygous or hemizygous for the hprt-null allele and homozygous nu/nu appear to have no phenotypic variation from standard Foxn1¹⁰⁻¹⁰ mice (Fig. 1A). To confirm genotyping (Fig. 1B, Supplementary Fig. S3), we harvested tail cuttings from mice II and III (Fig. 1A), trypsinized them, and grew the cells in tissue culture. These samples were grown in the presence of HAT or 6-thioguanine (6TG) to select for or against HPRT function, respectively (Fig. 1C). As predicted from their genotype (Fig. 1B), cells from the hprt-null mouse died in HAT media and survived in 6TG containing media. The HPRT-proficient heterozygous hprt-null/wt mouse cells gave the opposite result, as expected.

Patient-specific cancer cell line production

A PDA xenograft (Panc410) was implanted into these mice and the tumors were harvested for cell culture. After plating and 2 days of recovery, cultures of Panc410 (day 0) showed a mixture of cancer cells clustering together to form "islands" and scattered fibroblasts and other stromal cells (Fig. 2A and D). Cultures explanted from the hprt-null mouse and treated with HAT selection media typically yielded fibroblast-free cancer cell lines after 2 to 3 weeks (Fig. 2A–C). During this time, HAT selection eliminated the fibroblasts and other stromal cells, allowing for the small cancer cell "islands" to expand and eventually coalesce. In contrast, a sister culture, grown in the absence of HAT, was heavily contaminated with fibroblasts (Fig. 2D–F). These stromal cells surrounded cancer cell islands (Fig. 2E), overgrew them (Fig. 2F), and precluded producing cancer cell lines from these cultures. The resultant cell line matched the patient’s microsatellites and was tumorigenic in nude mice.
To confirm its epithelial origin, the cell line was stained for cytokeratin and smooth muscle actin, which stained positive and negative, respectively, as expected (data not shown).

Chemosensitivity-initial screen

One potential application of rapid cell line isolation is personalized chemosensitivity testing. To show use of the mice for this purpose, we first implanted SCID hprt-null mice with a surgically resected PDA and isolated the cell-line Panc502 (Supplementary Fig. S4). We then screened this cell line against the JHDL (13) consisting of 3,131 drugs (Supplementary Fig. S5). The library includes 1,907 U.S. FDA-approved drugs, 570 drugs approved for clinical use in other countries, and 654 other drugs in various phases of development. A histogram of the number of drugs, graphed as a function of the percentage of growth inhibition (Fig. 3A), showed that most drugs fit under a Gaussian distribution (mean, 5.0%; SD, 11.8%), which we interpreted as inactive drugs for this cancer cell line. The mean ± 3 SD encompasses 2,817 drugs or approximately 90% of those tested. More importantly, 314 drugs (~10%) showed activity above the normal distribution, and these were considered potentially active drugs (Supplementary Table S1). These 314 drugs included 77 drugs that are currently FDA-approved and 12 drugs previously approved but currently discontinued (combined ~2.8% of drugs in the library).

The FDA-approved drug, digoxin, showed 95% growth inhibition, consistent with its recent discovery as a potential antitumor agent (15). We also identified 2 terpenoid drugs, pristimerin and triptonide, isolated from Chinese medicinal plants, as potent inhibitors of growth (16–18). Among the 125 antineoplastic drugs tested (Supplementary Table S2), only a third (49 drugs, 39.2%) showed activity above the bell-shaped curve. Nine drugs showed greater than 99% growth inhibition, including 7 nucleic acid–targeting chemotherapeutics (actinomycin C, actinomycin D, chromomycin A3, camptothecin, doxorubicin, gemcitabine, and mitoxantrone) and 2 terpenoid natural products (pristimerin and triptonide).

Novel drugs with activity against PDA

From the drugs showing 75% or higher inhibition at 10 μmol/L final concentration, we selected 10 drugs to study further (Table 1), after excluding drugs with well-documented activity against pancreatic cancer, and those with relatively high toxicities (i.e., low LD50 values in mice). Only one of these drugs is FDA-approved. We generated dose–response curves to confirm activity and establish IC50 values for Panc502, Panc410, and another low-passage PDA cell line, Panc486, described below. From these, we selected 2 drugs because they showed significant variability in their IC50s among the 3 low-passage PDA cell lines (Fig. 3B). The anthracycline, nogalamycin, was approximately 11 × more effective against Panc502 than either Panc410 or the nontransformed pancreatic duct cell line, HPDE (data not shown). Finally, the cardiac glycoside digitoxin was substantially more toxic to Panc502 than Panc410, whereas Panc486 had an intermediate sensitivity. We also generated dose–response curves using a panel of topoisomerase inhibitors, showing that topoisomerase I inhibitors were generally more effective than topoisomerase II inhibitors (Supplementary Fig. S6).

Does in vitro chemosensitivity predict in vivo response?

To address the hypothesis that in vitro response could predict in vivo response, we then raised xenografted tumors from Panc410 and Panc502 cell lines and treated the mice harboring these xenografts with nogalamycin, digitoxin, or control for 30 days. We measured the size of tumors twice a week during this time (Fig. 3C). Both nogalamycin and digitoxin showed more activity against Panc502 than Panc410, supporting the notion that in vitro sensitivity does predict in vivo response, at least with these 2 drugs in these cell lines, as judged by tumor size (Fig. 3C), weight of the tumors after completing the treatment (Fig. 3D), and by visual inspection of the residual tumors after treatment (Supplementary Fig. S7).
Isolation of additional cell lines

To test whether we could use this system to routinely generate cell lines from solid cancers, we also isolated a cell line from an ovarian cancer, another highly lethal cancer. The ovarian cancer cell line, FM108, was established from an existing xenograft (Supplementary Fig. S8). We also isolated an additional cell line from a surgically resected PDA. Panc486 was isolated from a xenograft from a patient with a family history of pancreatic cancer (Supplementary Fig. S9). In each case, cell lines were documented to be tumorigenic in athymic mice, sequenced to document oncogenic mutations in the \( \text{Kras2} \) gene, and DNA finger-printed to confirm their patient origin (information available on request). During this time, we isolated 3 additional cell lines from other PDAs but were unable to produce cell lines from 2 other PDA xenografts using similar approaches.

### Table 1. Ten drugs with 75% or greater inhibition

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage of growth inhibition at 10 ( \mu \text{mol/L} ) on Panc502</th>
<th>( \text{IC}_{50} ), nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptolide (for triptonide)</td>
<td>98.1</td>
<td>7.3</td>
</tr>
<tr>
<td>Nogalamycin</td>
<td>75.4</td>
<td>23.3</td>
</tr>
<tr>
<td>Ouabain</td>
<td>95.6</td>
<td>39.7</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>95.1</td>
<td>62.7</td>
</tr>
<tr>
<td>Strophanthin K</td>
<td>98.9</td>
<td>69.3</td>
</tr>
<tr>
<td>Digoxin</td>
<td>94.7</td>
<td>70.8</td>
</tr>
<tr>
<td>Dithiazanine iodide</td>
<td>99.2</td>
<td>234.1</td>
</tr>
<tr>
<td>Strophanthinid</td>
<td>98</td>
<td>430.1</td>
</tr>
<tr>
<td>Quinacrine</td>
<td>100</td>
<td>657.7</td>
</tr>
<tr>
<td>Celastrol (for pristimerin)</td>
<td>100</td>
<td>753.6</td>
</tr>
</tbody>
</table>
components that were missing and remain to be identified.

Discussion

We report successful production of nude, SCID, and NSG immunodeficient mice whose hprt-null cells are biochemically selectable in vitro. Using this system, we were able to isolate 3 PDA and 1 ovarian cancer cell line. The Panc502 familial PDA cell line was isolated directly from the tumor surgically resected from a patient, and we screened it against a panel of 3,131 drugs. Approximately 314 drugs show potential activity, where the vast majority of them (265, 84%) were not designated as antineoplastics. Of 125 antineoplastic drugs, only 49 (39%) showed activity. Two novel drugs showed selective activity in vitro, and this correlated with in vivo response. We also identified 2 terpenoid drugs with more than 99% growth inhibition.

In this article, we describe an alternative strategy to traditional CSRAs. In contrast to traditional CSRAs, the approach described herein uses: (i) pure low-passage human cancer cells, (ii) cells that are viable and well-adapted to in vitro growth, and (iii) larger drug panels. The use of pure cancer cells means that any signal detected is due to the drug's effect on the malignant cells rather than stromal cell toxicity. Because the cancer cells are growing and healthy, measured effects are a combined effect of the drug and the cancer cells and not due to synergistic effects of the drug with anoxia, starvation, overnight shipping, etc. Finally, because the cells are expanded into a low-passage cell line, drug panels with thousands of drugs can be screened, rather than the 5 to 10 typically tested in traditional CSRAs. This permits one to test all FDA-approved antineoplastics, FDA-approved drugs for other indications, late-phase clinical trial drugs, herbal drugs, and drugs approved in other countries for clinical use. The idea of screening drugs using cancer cell lines is well established (reviewed in ref. 19), and the personalized approach has recently been validated for one patient with a rare type of pancreatic cancer, acinar cell carcinoma (20).

The approach described herein differs from the xenograft-based approach show by Hidalgo's group (21, 22). The advantage of the low-passage cell line approach is that more drugs can be screened under highly controlled conditions. A possible advantage of the xenograft approach is that xenografted tumor response may be more biologically predictive of response in patients. We are eager to test whether low-passage personalized cell line responses can predict patient response. This may be best tested with a malignancy for which several alternative first-line chemotherapeutic choices are available.

Drugs with activity in vitro may not be limited to those that show more than 95% growth inhibition. While digoxin showed 95.1% growth inhibition in vitro, nogalamycin was chosen, in part, because it only had 75.4% growth inhibition in vitro. Finally, it is possible that the drugs identified could be synergistic with those currently in clinical use, such as gemcitabine, although this remains to be shown. In the future, the combination of the patient's germline single-nucleotide polymorphisms (SNP), somatic mutations, mRNA expression, and epigenetic changes in the cancer may play an increasing role in the choice of chemotherapy. Despite this, one can also imagine a role for functional CSRAs. This is currently being attempted for various cancers (23–26), although it is controversial whether this testing is truly predictive of in vivo response (2, 3). This initial sample took about 8 months from surgical resection to full drug panel testing; however, we estimate that, with additional optimization, this testing could be accomplished much sooner. The shorter time could be achieved by implanting more mice, with additional experience, and most importantly by using robotics for the drug screening. Certain clinical settings, such as identifying drugs after a Whipple procedure for PDA, might be especially amenable to this time frame. Applying a similar approach to a cohort of genetically defined cell lines could define a standardized core set of drugs to be tested on all resected PDAs.

Cell lines are useful for many other studies of cancer biology as they: (i) can be expanded indefinitely, (ii) contain all of the gene mutations present in the patient's primary cancer, (iii) can be manipulated in vitro by adding or eliminating genes, (iv) can be implanted in mice to test the effects of these manipulations on the ability to form tumors (21, 27), and (v) carry few if any additional genetic changes from the primary cancer (28). Cancer cell lines are also important for other in vitro functional studies, molecular imaging, and possibly isogenic cancer vaccine production. With increasingly powerful tools such as whole-genome DNA sequencing, RNA interference libraries, and high-throughput drug screens, one can anticipate that the need for cell lines from human cancers will likely increase (13, 29–31).

We envision several applications of this system for cancer cell line production. First, there are no cell lines representing some malignancies, such as oligodendrogliomas and pheochromocytomas, and in others, such as esophageal, thyroid, and salivary gland tumors, many cell lines are contaminants (32). For others, such as prostate, ovarian, and breast cancers, the number of available cell lines cannot fully represent the full spectrum of disease (e.g., most existing prostate cancer cell lines are hormone-refractory). In addition, some cancers contain unique genetic defects, and successful cell line production is essential to identify pathway members, and perhaps most importantly, for high-throughput drug screening.

There are some limitations of this system. For some cancers, stromal cells from the tumor microenvironment may provide paracrine growth stimuli to the malignant cells, and this may explain why we were unable to isolate 2 of the cell lines. It is generally believed that all of the human stromal cells are replaced by mouse stromal cells in a single passage in immuno-defective mice. While we
generally agree with this assessment based on phase microcopy of HAT-treated cultures (unpublished data), this has never been formally quantified. The replacement of stromal cells may be slightly less than 100% based on the extremely faint residual PCR product from DNA isolated from xenografts of cancers containing homozygous deletions (33). In this regard, it is possible that some tumors may need to be passed through additional mice to get complete replacement of the human stromal cells. It is also possible that some cancers require unique cytokines that are not currently components of tissue culture medium.

In addition to cell line production, one can envision other situations where an animal model is required to study a biologic process but where recovery of the exogenous cells is subsequently required. For example, the mouse may be useful for isolation of organ-specific spontaneous metastases or small numbers of dormant malignant cells refractory to chemotherapeutic agents. Finally, high-throughput functional chemosensitivity profiling may be especially warranted for those patients who have failed conventional chemotherapeutic options.

Disclosure of Potential Conflicts of Interest

S. Rauenzahn, A. Maitra, and J.R. Eshleman may receive royalty payments if the mice are licensed; a patent licensed to Myriad Genetics (R.H. Hruban and J.R. Eshleman); and Advisory Board membership in Roche Molecular Diagnostics (J.R. Eshleman). No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: S. Rauenzahn, M. Hidalgo, R.H. Hruban, A. Maitra, J.R. Eshleman

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References


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