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Review

Establishment of Drug-resistant Cell Lines as a Model in Experimental Oncology: A Review

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Abstract. *Many types of cancer are initially susceptible to chemotherapy, but during treatment, patients may develop resistance to therapy. Knowing that acquisition of drug resistance is a major clinical problem in antineoplastic treatment, the present work aimed to present, through a literature review, the development of chemoresistant cells lines as a model in experimental oncology. A total of 110 drug-resistant cell lines, mainly from lung tumors and leukemias, have been developed. In addition, it has been observed that the drugs used for induction of resistance represented the drugs used for first-line treatment of each neoplasia, since the ideal chemotherapeutic treatment to induce resistance in vitro aims at a better modulation of the therapeutic response in order to better study the mechanisms of resistance.*

Normal tissue controls the production and release of growth promoting signals that regulate the initiation and progression of the cell cycle, ensuring cellular homeostasis and maintainance of healthy tissue architecture and function. Cancer cells exhibit deregulation of these signals and may acquire the ability to maintain continuous and abnormal proliferative signaling, inhibition of growth suppressors, resistance to cell death, replicative immortality, angiogenesis and metastasis that leads to an inadequate and pathogenic functioning of the tissue in which they occur (1-4).

The literature shows that, in the tumor model, cancer cells originate from a single cell that has important stem cell characteristics, including the unlimited potential for replication and mechanisms of protection from xenobiotic agents. These findings have a significant effect on cancer treatment, since traditional antineoplastic treatment was based on the assumption that all somatic cells have a similar malignant potential, and the lack of specificity in combating these characteristics has rendered the therapies ineffective in providing a lasting response to cancer (5, 6).

Chemotherapy is one of the pillars of clinical cancer treatment, but its outcome usually culminates in multidrug resistance (MDR), a phenomenon that can be found in several cells present in the tumor microenvironment, drastically restricting and the curative effect of drugs for a variety of tumors (7-9).

Although many types of cancer are initially susceptible to chemotherapy, over the course of the therapeutic regimen, some patients may develop therapeutic resistance, due to several intracellular mechanisms including genetic and epigenetic changes in signaling pathways of survival, drug metabolizing enzymes and drug efflux pump mechanisms. Epigenetic modifications also act as an important set of mechanisms that lead to resistance in cancer treatment, and the main ones include DNA methylation and histone acetylation that can influence carcinogenesis because they deregulate normal expression of genes (Figure 1) (10, 11). The most studied mechanism of resistance to drugs against cancer involves the reduction of the intracellular concentration of the drug by increasing drug efflux outside the cell. In addition, the damaged DNA repair mechanism plays a very important role in the resistance to antineoplastic drugs, since, in response to chemotherapeutic

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Table I. *Panel of solid and hematopoietic tumour cell lines - NCI-60.*

Solid and hematopoietic tumours	
Tumour type	Cell lines
Prostate	DU-145; PC-3
Kidney	786-0; A498; ACHN; CAKI-1; RXF 393; SN12C; TK-10; UO-31
Breast	T-47D; BT-549; HS 578T; MDA-MB-468; MDA-MB-231/ATCC; MCF7
Ovary	IGR-OV1; OVCAR-3; OVCAR-4; OVCAR-5; OVCAR-8; NCI/ADR-RES; SK-OV-3
Central nervous system	SNB-19; SNB-75; U251; SF-539; SF-295; SF-268; SNB-78; XF-498.
Colon	SW-620; KM12; HT29; HCT-15; HCT-116; HCC-2998; COLO 205
Melanoma	SK-MEL-5; SK-MEL-28; UACC-257; UACC-62; SK-MEL-2; MDA-MB-435; M14; MALME-3M; LOX IMVI; U251; RPMI-7951; M19-MEL; DLD-1; KM20L2
Non-small cell lung	NCI-H522; A549/ATCC; EKVX; HOP-62; HOP-92; NCI-H226; NCI-H23; NCI-H322M; NCI-H460; LXFL 529; DMS 114; SHP-77
Leukemias	P388/ADR; P388; K-562; SR; RPMI-8226; MOLT-4; CCRF-CEM; HL-60 (TB)

drugs that directly or indirectly damage DNA, DNA damage response mechanisms can reverse drug induced damages (6-10).

The acquisition of resistance to chemotherapeutic treatments in cancer patients is a major clinical problem and remains a critical obstacle in anti-neoplastic treatment. Therefore, the elucidation of the underlying pleiotropic mechanisms involved in the phenotype of resistance to substances used to treat different tumor types is essential for the development of new strategies effective in overcoming resistance phenomena (12).

Application of Cell Lines in Experimental Oncology

Experimental oncology is defined by studies that aim at the analysis and understanding of carcinogenesis, sometimes induced in experimental animal models with the use of physical, chemical, natural carcinogens or biological agents. In addition, experimental oncology supports clinical oncology, by studying oncolytic or oncostatic effects of artificial (drug) or natural (hormones) chemicals in tissue or cell cultures (13).

From 1985 to 1990, the National Cancer Institute (NCI) of the United States of America estabished a screening program for antitumor molecules, at this point, a murine cell line P388 was applied to study the mechanisms, tumor biology and carcinogenic modifications in tumors of human origin. However, since 1990, this program has been withdrawn and, as a substitute, a new *in vitro* primary screening was developed based on a panel of different tumor cell lines derived from human biopsies (14).

This initial panel comprised about 60 different cell lines derived from tumor biopsy specimens from patients with solid tumors and hematological malignacies, and was named NCI-60. The main purpose of this program was the identification of compounds with the capacity to inhibit tumor growth in culture. It also supports studies focusing on understanding tumor biology and those developing new drugs with more specific antitumor potential. Although the NCI-60 cell panel alone did not lead to the discovery of paradigm-shifting compounds within the anti-neoplastic treatment, this panel encouraged a number of research programs, particularly those related to cytotoxic chemotherapy and to the discovery of drugs (15).

However, as knowledge of cancer biology has been expanding, attention has been given to several other properties of malignant cells that can be used as targets for the development of antineoplastic drugs such as the DNA repair process (16), cell differentiation (17), synthetic lethality (18), angiogenesis (19) and epigenetic modification (20).

For this reason, there has been a recent enlargement of the panel of solid and hematopoietic tumor lines with the addition of 13 additional lines that now constitute the NCI-60 panel, last updated in 2015 (21) (Table I).

Tumors are complex tissues, composed of multiple distinct cell types that participate in heterotypic interactions with each other, and about 85% of human cancers are from solid tumors (22). Breast, prostate, liver, pancreas, and lung cancer, among others, are examples of these types of neoplasias (23).

Due to the increasing incidence of solid tumors over the years, it has been and continues to be necessary to establish new methods for studying the biology of these types of cancer as well as the mechanisms that limit antineoplastic therapy in order to improve future treatment (24).

Hematologic cancers, consisting of leukemia, lymphoma, and myeloma, originate and progress in primary or secondary lymphoid organs and develop and spread differently from solid tumors (25). The main characteristic of these types of cancer is their ability to affect bone marrow hematopoietic precursors that, from the beginning, are no longer restricted to a single region of the body, manifesting

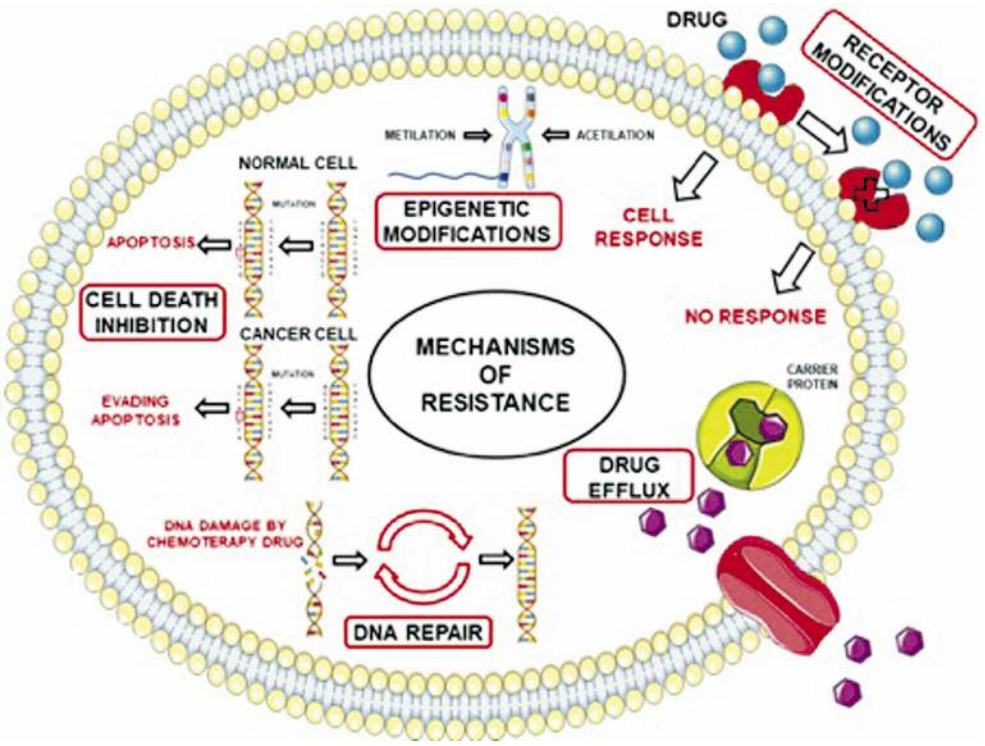

Figure 1. *Mechanisms that can activate or promote resistance of cancer cells to chemotherapeutic agents.*

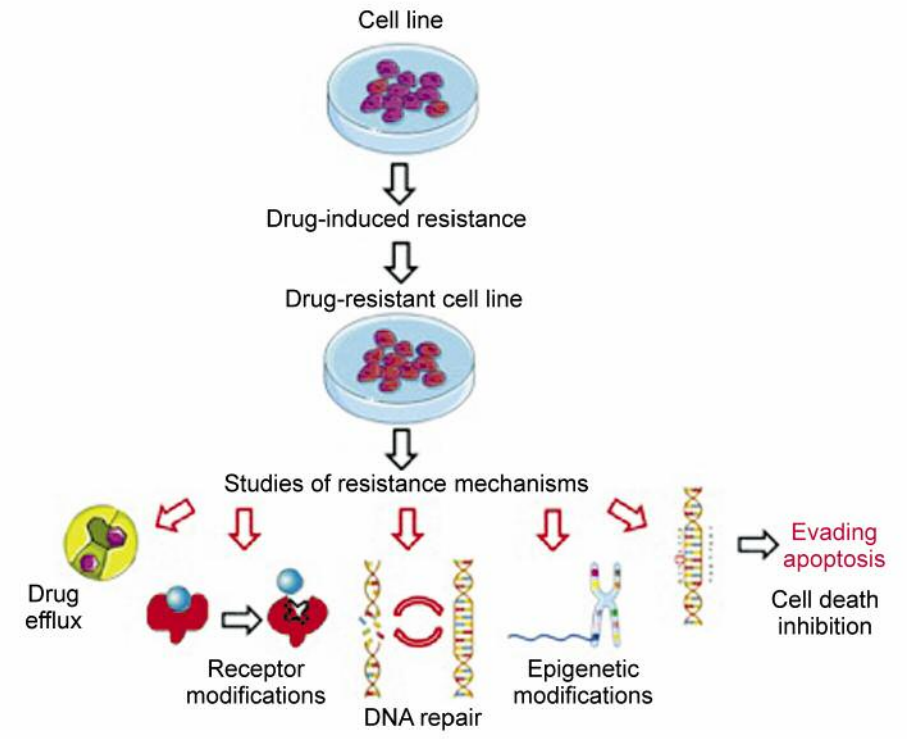

Figure 2. *Establishment of a drug-resistant cell lines with increasing concentrations of a certain drug to study the biological changes leading to resistance mechanisms.*

Table II. *Establishment of drug-resistant cell lines of solid and hematopoietic tumours, described in the literature.*

Tumour type	Original cell lines	Resistance induction	Drug-resistant cell lines	Performed studies	Reference
Osteosarcoma	SOSP-9607 Saos-2 *[1]MNNG/HOS; [2,3]MG63 [4]HOS	Cisplatin (CDDP) Adriamycin (ADM) [1,2]Doxorubicin (DXR) [3,4]Methyl-pirophosphate-α (MPPa-PDT)	SOSP-9607/CDDP Saos-2/ADM1; Saos-2/ADM4 [1]MNNG/HOS/DXR1000 [2]MG63/DXR1000 [3]MG63/PDT; [4]HOS/PDT	• Hyperexpression of drug efflux proteins (MDR1 and MRP) • DNA synthesis in the established cell line.	HAN *et al.* (36) NIU *et al.* (37) [1,2]ODA *et al.* (38) [3,4]TAO *et al.* (39)
	OST	Cisplatin (CDDP)	OST/R		ASADA *et al.* (40)
Gastric adenocarcinoma	[1,2,3,4,5,6]OCUM-2M	[1]5-Fluorouracil (5FU), [2]Paclitaxel (PTX), [3]Oxaliplatin (OXA) [4]Irinotecan (SN38) [5]Gemcitabine (GEM) [6]Cisplatin (CDDP)	[1]OCUM-2M/5FLU [2]OCUM-2M/PTX [3]OCUM-2M/OXA [4]OCUM-2M/SN38 [5]OCUM-2M/GEM [6]OCUM-2M/DDP	• Study of the expression of genes related to drug resistance; cell death by apoptosis in drug-resistant cell lines and cross-resistance to other anticancer drugs.	[1,2,3,4,5]ZHANG *et al.* (41) [6]NITTA *et al.* (42) FELIPE *et al.* (43)
	AGS SNU638	Epirrubicina (EPI) 5-Fluorouracil (5FU)	AGS/EPI 638-F1; 638-F2	• Study of the biological and biochemical characteristics of the resistant cell lines in relation to the parental.	CHUNG *et al.* (44)
Hepatocellular carcinoma	HLF	5-Fluorouracil (5FU)	HLF-R4; HLF-R10	• Cross-resistance studies to other drugs and expression of MDR-related genes.	UCHIBORI *et al.* (45) ZHOU *et al.* (46)
	SK-Hep-1	Cisplatin (CDDP)	SK-Hep-1/CDDP		
Multiple myeloma	U266	Bortezomibe	U266/velR	• Gene expression analysis to assess the profile of expression changes resulting from bortezomib resistance.	PARK *et al.* (47)
Breast	[1,2]MCF-7	[1]Paclitaxel [2]Paclitaxel	[1]MCF-7/Taxol [2]MCF-7/TAX	• Determination of cell cycle distribution; Expression of breast cancer-related MDR proteins and cross-resistance evaluation.	ZUO *et al.* (48) CHEN *et al.* (49)
	MDA-MB-231	5-Fluorouracil (5FU)	MDA-MB-231/5-FU	• Cross-resistance profile study; Measurement of P-glycoprotein and uptake	TAKAHASHI *et al.* (50)
	FM3A	NC-190	FM/NC-R	of NC-190 and analysis of Topoisomerase II.	SAMATA *et al.* (51)
Pancreas	PANC-1	Gemcitabine (GEM)	PANC-1RG7	• Analysis of the cell cycle and analysis of genes and proteins associated with resistance.	WANG *et al.* (52)
Bladder	BFTC-905 MGH-U1	Doxorubicin Doxorubicin	BFTC-905–DOXO-II MGH-U1R	• Study of atypical mechanism of resistance and analysis of the overall gene expression profile	GREIFE *et al.* (53) MCGOVERN *et al.* (54)
	KK47	Doxorubicin	KK47/ADM	of the established cell line in comparison with the parental. • Characteristics of celll line growth and karyotype analysis. • Cross-resistance and studies of uptake and efflux of drug that induced resistance.	KIMIYA *et al.* (55)
Bile ducts	[1]KKU-M139 [2]KKU-M214	[1,2]Gemcitabine (GEM)	[1]KKU-M139/GEM [2]KKU-M214/GEM	• Cross-resistance study as well as cell adhesion, migration and invasion capacity of the cell line. • Cell cycle analysis and study of apoptotic evasion mechanisms.	[1,2]WATTAN-WONGDON *et al.* (56)
Leukemias	[1,2,3]MOLM-13	[1]Azacitidine [2]Decitabine [3]Methotrexate (MTX)	[1]MOLM/AZA-1 [2]MOLM/DEC-5 [3]MOLT-3/MTX	• Cytogenetic characterization, expression of cancer-related and phenotypic	[1,2]HUR *et al.* (57) [3]OHNOSHI *et al.* (58)
	THP-1 [1,2,3,4,5,6]K562	Etoposideo (VP-16) [1]12-O-tetradecanoylphorbol 13-acetate (TPA)	THP-1/E [1]K562/TPA	evaluation of established resistant cell lines. • Cytoskeleton alterations and	SAIJO *et al.* (59) [1]TAKEDA *et al.* (60)

Table II. *Continued*

Table II. *Continued*

Tumour type	Original cell lines	Resistance induction	Drug-resistant cell lines	Performed studies	Reference
		[2]Adriamycin (ADM) [3]Trióxido de arsênio (As2O3) [4]Vincristine [5]Daunorrubicin [6]Decitabine (5-aza-2-deoxycytidine, DAC)	[2]K562/A02 [3]K562/AS-3 [4]K562-Lucena1 [5]K562-FEPS [6]K562/DAC	influence of MDR phenotype in the assessment of the potential of mitochondrial transmission • Determination of expression and activity of ABC transporters and determination of cell viability in the treatment with MDR modulators; Expression of Bcl-2 and P53; Effect of extracellular ATP and ATP effect on cell viability. • Evaluation of apoptosis rates and study of the expression of genes related to resistance	[2]LUAN (61) [3]SEO *et al*. (62) [4]RUMJANEK *et al*. (63) [5]SILVA (64) [6]WEN *et al*. (65)
	MYL	Imatinib Mesylate	MYL-R		ITO *et al*. (66)
Spinocellular carcinoma	[1]HSC2 [2]HSC4	[1,2]5-Fluorouracil (5FU)	[1]HSC2/FU [2]HSC4/FU	• Study of the effects of 5-Fluorouracil on apoptosis and evaluation of E-cadherin, N-cadherin and Twist expression.	[1,2]HARADA *et al*. (67)
	H-I	Cisplatin (CDDP)	H-IR		NAKAMURA *et al*. (68)
	EC109	Cisplatin (CDDP)	EC109/CDDP	• Expression levels evaluation of normal and carcinogenic tissue genes as well as MDR related genes.	WEN *et al*. (69)
	A431	Cisplatin (CDDP)	A431/CDDP1; A431/CDDP2		MESE *et al*. (70)
	Sa-3	Cisplatin (CDDP)	Sa-3R		NAKATANI *et al*. (71)
	[1,3,4]KB [2]Hepd	[1,2]Bleomycin (BLMr) [3]Cisplatin (CDDP) [4]Cisplatin (CDDP)	[1]KB-BLMr [2]Hepd-uvBLMr [3]KB-R [4]KB-rc cell 53	• Cellular and morphological alterations; Analysis of cell cycle distribution and expression levels of MDR-related genes.	[1,2]URADE *et al*. (72) [3]NEGORO *et al*. (73) [4]HORI *et al*. (74)
Head and neck	[1]Hep-2 [2]CAL-27	[1,2]Cisplatin; [1,2]Docetaxel; [1,2]5-Fluorouracil	[1]Hep-2 TPF resistente (TPFR) [2]CAL-27 TPFR	• Analysis of the effect of drug treatments on cell viability, apoptosis, cell cycle and gene expression associated with MDR.	[1,2]GOVINDAN *et al*. (75)
	[1]LICR-HN2 [2]LICR-HN5 [3]SC263	[1,2,3]Cetuximabe	[1]LICR-HN2 R10.3 [2]LICR-HN5 R9.1 [3]SC263 R10.2		[1,2,3]BOECKX *et al*. (76)
	HLac 79	Cisplatin (CDDP)	DDP1-DDP1 DDP1-DDP2 DDP1-DDP3 DDP1-DDP4	• Analysis of the gene expression of resistant cells; Study of EMT characteristics • Study of glutathione metabolism and analysis of drug uptake.	BIER *et al*. (77)
	[1,2,3]SCC-1	[1]Cetuximab [2]Gefitinib [3]Erlotinib	[1]Cet-R [2]Gef-R [3]Erl-R	• Epidermal growth factor receptor (EGFR) signaling study of EGFR inhibitor resistant cells.	[1,2,3]BENAVENTE *et al*. (78)
Mantle cell lymphoma	KPUM-YY1	Bendamustine Hydrochloride	KPUM-YY1R	• Cross-resistance study; Analysis of the cytogenetic and molecular characteristics of the strain and analysis of gene expression.	TAKIMOTO-SHIMOMURA *et al*. (79)
Ovary	NOY1	Cisplatin	NOY1-CR	• Expression of anti-apoptotic proteins; Mechanisms of cisplatin resistance.	SHIBATA *et al*. (80)
	KF-1	Cisplatin	KFr		KIKUCHI *et al*. (81)
	NOS2	DWA2114R	NOS2CR1 NOS2CR2	• Study of lactate dehydrogenase (LDH) activity and isoenzyme analysis.	MISAWA *et al*. (82)
Cervical cancer	HeLa	[1]Aplidin (APL) [2]Bleomicin (BLMr)	[1]HeLa-APL [2]HeLa-BLMr	• Cell cycle and apoptotic pathways; Analysis of P-glycoprotein expression and cross-resistance analysis. • Analysis of the degree of resistance and stability of this phenotype.	[1]LOSADA *et al*. (83) [2]URADE *et al*. (72)

Table II. *Continued*

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Tumour type	Original cell lines	Resistance induction	Drug-resistant cell lines	Performed studies	Reference
Endometrial carcinoma	HHUA	5-Fluorouracil (5FU)	5FUr-3C; 5FUr-3D; 5FUr-4A; 5FUr-10B	• Cross-resistance study to other anticancer drugs; Suppression of DNA fragmentation; Karyotyping	TANAKA *et al*. (84)
Lung	[1,3,4]PC-9 [2]A549	[1,2]Pemetrexedo (PEM)	[1]PC9/PEML1; PC9/PEML2; PC9/PEMH1; PC9/PEMH2;	• Gene expression encoding thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycolamide ribonucleotide	[1,2]ZHANG *et al*. (85)
		[3]Mitomycin C	[2]A549/PEML1; A549/PEML2;	formyltransferase (GARFT) and cross-resistance analysis.	[3]SHIBATA *et al*. (86)
		[4]Gefitinib	A549/PEMH1; A549/PEMH2	• Resistance mechanisms through hyperexpression of the MDR1 gene;	
			[3]PC-9/MC2; PC-9/MC4	Analysis of intracellular glutathione levels (GSH), pi glutathione	[4]KOIZUMI *et al*. (87)
			[4]PC-9/ZD	S-transferase (GST) and	
	PC-7	Camptothecin-11 (CPT-11)	PC-7/CPT	Topoisomerase II activity.	KANZAWA *et al*. (88)
	[1,2,3,4,5]SBC-3	[1]7-etil-10-hydroxy-camptotecina (SN-38)	[1]SBC-3/SN-38	• Cross-resistance study and analysis of mechanisms that confer resistance to drugs.	[1]KANZAWA *et al*. (89)
		[2]Adriamycin (ADM)	[2]SBC-3/ADM		
		[3]NB-506	[3]SBC-3/NB # 9	• Studies of intracellular drug accumulation; Studies of drug uptake, revealing decreased influx and increased efflux in resistant cells and cytogenetic analysis.	[1]CHIKAMORI *et al*. (90)
		[4]Adriamycin (ADM)	[4]SBC-3/ADM100		[2]MIYAMOTO *et al*. (91)
		[5]DX-8951f	[5]SBC-3/DXCL1		[3]YOON *et al*. (92)
				• Analysis of Topoisomerase I and II activity.	[4]KIURA *et al*. (93)
					[5]NOMOTO *et al*. (94)
	H460	Cisplatin	H460/CIS		YOON *et al*. (92)
	H69	Ocadaic Acid (AO)	H69/OA100		TAKEDA *et al*. (95)
Colon	THC8307	Oxaliplatin	THC8307/L-OHP	• Analysis of differentially expressed genes, revealing that pro-apoptotic genes are overexpressed.	TANG *et al*. (96)
	[1,2,3]HCT-15	[1,2,3]Adriamycin	[1]HCT-15/ADM1 [2]HCT-15/ADM2 [3]HCT-15/ADM2-2		UCHIYAMA-KOKUBU *et al*. (97)
	KM12	R115777	KM12/R115	• Cross-resistance study and evaluation of the expression of MDR-associated genes.	SMITH *et al*. (98)
Neuroblastoma	[1]TGW [2]TOGO	[1,2]Cisplatin	[1]TR1, TR2, TR3 [2]GR2 e GR3	• Cytotoxicity analysis and evaluation of expression levels of MDR1, MRP1, hMLH1 and hMSH2 genes.	[1,2]IWASAKI *et al*. (99)
Prostate	[1]DU145 [2]PC-3	[1,2]Paclitaxel	[1]DU145-TxR [2]PC-3-TxR	• Mechanisms of hyperexpression of MDR1;	[1,2]TAKEDA *et al*. (100)
				• Silencing of MDR1 and analysis of mechanisms of resistance;	
Kidney	RCC8701	Adriamycin	RCC8701/ADR800	• Cell cycle analysis; Evaluation of MDR1 gene expression, glutathione transferase (GST-π) and topoisomerase II and cross-resistance study.	YU *et al*. (101)
Germ cells	GCT27	Cisplatin	GCT27cisR	• Cross-resistance study; Cytogenetic analysis and study of mechanisms of resistance to acquired cisplatin involving reduction of intracellular accumulation and analyzes of GSH and Metallothionein levels.	KELLAND *et al*. (102)

[1,2,3,4,5,6]Superscript numbers refer to the combination of each parental cell line, correspondent drug and derived resistant cell line.

themselves in several parts without respecting anatomical barriers (26).

Advances in the biological understanding of these types of hematological malignancies are important for the development of more selective and effective treatments, and overcoming resistance mechanisms (27).

Pharmacokinetic factors such as absorption, distribution, metabolism and elimination may limit the amount of systemically administered substance until reaching the cancer cells. In the tumor environment, the effects of drugs on malignant neoplastic cells may be limited by poor drug influx or excessive efflux; inactivation of susbstance and also by inhibition of apoptosis (28).

Establishment of Drug-Resistant Cell Lines

Studies on the mechanisms of cytotoxicity and resistance to chemotherapy in experimental oncology are based on the development and analysis of resistant cancer cell lines (29). In this context, the establishment of resistant tumor cell lines has been used to obtain information on the possible mechanisms that promote the evolution of malignancy, since they provide useful biological models for the study of tumors presenting phenotypes of multiple drug resistance (MDR) (30).

MDR is considered a multifactorial phenomenon and occurs mainly as a result of hyperexpression of transporters of the superfamily of ATP binding cassette proteins (ABC transporters) (31), a large family of proteins that uses the energy of hydrolysis of ATP to actively expel the drug out of cells (32). Thus, many current studies concentrate on trying to suppress MDR, for a more effective therapy against cancer.

Cell lines developed as models of resistance, particularly through the administration of a certain chemotherapeutical drug that is commonly used in clinical practice, are used to study and understand MDR to develop strategies to overcome it. Therefore, well-characterized chemoresistant cell lines, preferably originating from a common sensitive parental cell line, need to be developed (Figure 2) (33, 34).

One of the first studies in the establishment of an MDR cell line was conducted in 1983 by Tsuruo and co-workers. In vitro induction of resistance of the K562 cell line, a human erythroleukemia cell line, was performed through exposure to increasing vincristine doses from 3 nM to 60 nM, which is the concentration used in clinical practice for the treatment of leukemias. This study made it possible to evaluate *in vitro* the mechanisms involved in MDR (35).

Thus, the objective of this work was to identify solid and hematopoietic tumor models of chemoresistant cell lines, which have been developed to understand the phenomenon of resistance to chemotherapeutics, commonly seen as a model of evolution in cancer and as a tool for the discovery of new drugs which may be more effective against cancer.

Results and Discussion

Table II shows the establishment of a total of 110 drug-resistant cell lines of solid and hematopoietic tumors by drug induction, besides the established drug-resistant cell lines, which were the parental lines used for induction of resistance *in vitro*.

The number of drug-resistant cell lines that was established from solid tumors was higher than that from hematopoietic tumors, resulting in a total of 97 cell lines. Only 13 established resistant cell lines derived from hematopoietic tumors. Of these, 11 cell lines correspond to leukemic tumors, one to the mantle cell lymphoma tumor and one strain to multiple myeloma.

The most frequent solid tumor for the establishment of chemoresistant lines was the pulmonary type, and although there was a significant heterogeneity between strains derived from the lung tissue, the SBC-3 parental cell line was the most frequently used in comparison to others. Therefore, it is suggested that the SBC-3 cell line is a good model for *in vitro* resistance induction (89-95).

Lung cancer is the leading cause of cancer-related death worldwide and is classified into two major subtypes: non-small cell lung cancer, which accounts for approximately 85% of all lung cancers, and small cell lung cancer diagnosed in 15% of cases (103, 104).

Although lung cancer treatment has progressed over the years, the 5-year survival rate remains low, largely due to the emergence of resistance before and during the course of chemotherapy and radiotherapy (105), and this resistance to antineoplastic therapy contributes significantly to the progression of the disease, its recurrence and mortality (106, 107). The discovery of the resistance mechanisms and strategies to suppress resistance to chemotherapy is very important for lung cancer therapy, especially in advanced cancers (108, 109).

Leukemia has also been proven to be a very frequent tumor type used for the establishment of drug-resistant cell lines; among the different parental cell lines used to develop resistance, the K-562 was the most frequent (60-65).

Leukemia is a type of malignant clonal disease originating from hematopoietic stem cells and can be classified into two categories: myeloid and lymphoid and, according to the stage of maturation, as acute or chronic (110). With the advancement of chemotherapy, hematopoietic stem cell transplantation, immunotherapy and molecular therapy, many patients with leukemia may achieve complete remission (111-113), however, most patients end up failing during treatment, including chemotherapy (114, 115).

Recent studies have shown that resistance to chemotherapy in most cases remains a major factor for failure of anti-neoplastic treatment, resulting in short-term survival of patients with leukemia (115). Thus, it is necessary

to develop new treatment strategies that target the mechanisms that lead to resistance, which will consequently be more effective (116).

Leary *et al*. have demonstrated that several molecular inhibitors, including P-glycoprotein inhibitors, used in combination with cytotoxic substances, were able to prevent the development of MDR in different *in vitro* and *in vivo* model systems (117).

However, based on these studies, it was possible to emphasize that the development of chemoresistant cell lines from pulmonary tissue, leukemia and other tumor types aims not only to understand resistance mechanisms, but also to identify tools to overcome MDR; although no targeted treatment has been developed by using the chemoresistant cell lines presented in Table II, their development aims also to aid in the screening of new drugs that are able to overcome mechanisms of resistance to chemotherapeutics and be effective in reversing resistance in patients that are refractory to available therapies (57-66, 85, 87-93).

Although lung tumors and leukemias were the most frequent models used for the development of drug-resistant cell lines, the presence of less frequent tumor types, such as bladder and kidney, also shows the importance of studying chemotherapy resistance mechanisms by inducing cell lines derived from these tumor types through the use of chemotherapy drugs, since this methodology has been proven to be the most appropriate for the study of cells that acquire mechanisms of resistance (118, 119).

However, the drugs used for induction of resistance were not randomly selected drugs. It was observed that the drugs used, in most cases, represented the drugs used in the first line treatment of each neoplasia, since the ideal chemotherapeutic treatment to induce resistance *in vitro* is the one that elicits the best therapeutic response, in order to study, in a more adequate manner, the mechanisms of resistance.

The main drugs used to establish the drug-resistant cell lines were cisplatin (CDDP) and adriamycin (ADM). Cisplatin was the drug mostly used for the induction of chemoresistant lines from tumors of spinocellular origin (36-38, 40, 42, 46, 53-55, 61, 68-71, 73-75, 77, 80, 81, 91-93, 97, 99, 101, 102).

The increased incidence of cisplatin use may be associated with the fact that cisplatin-based chemotherapeutic regimens are the most commonly used (neo) adjuvant treatments for most solid tumors; although platinum-based chemotherapeutic regimens have been shown to be effective against highly proliferative malignancies, significant rates of relapse and progression, as well as decreased overall survival and resistance are still observed (120).

The therapeutic failure due to the acquisition of resistance in patients undergoing antineoplastic treatment is the major problem which has resulted in higher numbers of deaths. However, understanding of these resistance mechanisms is important in order to design strategies to overcome this problem. For this, drug-resistant cell lines models provide us with valuable *in vitro* tools to elucidate the mechanisms underlying clinical resistance to anticancer drugs and to identify clinically significant biomarkers (121).

Conclusion

The establishment of *in vitro* models that resemble the multifactorial resistance process observed *in vivo* is crucial, and drug-resistant cell lines are, so far, good models for understanding the resistance process in tumor cells and, consequently, for screening new drugs, in order to circumscribe the mechanisms of resistance found in the clinical context.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Amaral MVS, Portilho AJS and Moreira-Nunes CA performed the study design; Silva EL, Sales LO and Moreira-Nunes CA prepared the figures; Amaral MVS, Portilho AJS, Maués JHS, Moraes MEA and Moreira-Nunes CA wrote the article; Sales LO, Maués JHS and Moreira-Nunes CA revised the final version. All Authors read and approved the final article.

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