Sameer Ullah Khan
Fayaz Malik *Editors*

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To all those who have faced the persistent challenge of cancer with unwavering courage, whose resilience and strength continue to inspire our pursuit of innovative solutions.

In memory of those who fought courageously, and in honor of those who endure, may our collective efforts lead to a future where cancer drug resistance is conquered, and hope prevails.

This book is dedicated to you—The Warriors in the Battle Against Cancer.

Dr. Sameer Ullah Khan and Dr. Fayaz Malik.

Preface

Cancer, with its complex combination of genetic mutations and cellular complexities, continues to challenge the boundaries of medical science. Despite remarkable progress in understanding the molecular underpinnings of cancer and the development of diverse therapeutic approaches, the phenomenon of drug resistance persists as a challenging hurdle in the pursuit of effective cancer treatment. The book you hold in your hands, *Drug Resistance in Cancer: Mechanisms and Strategie*s, is a concerted effort to elucidate the perplexity of drug resistance in cancer and present innovative strategies to confront this challenge. The journey through these pages is a comprehensive exploration of the mechanisms that cancer cells employ to resist the treatments designed to eradicate them. From the introductory chapters laying the groundwork for the understanding of drug resistance to the specialized discussions on cancer stem cells, immune cell dynamics, and the intricate interplay within the tumor microenvironment, each section is crafted to offer profound insights into the diverse aspects of this intricate problem.

The chapters committed to elucidating the roles of epigenetic alterations, metabolic reprogramming, and intracellular compartments underscore the intricacies of cancer biology and the adaptability of malignant cells to therapeutic pressures. The exploration of autophagy's dual role and the unexpected influence of gut microbes expand the horizons of our comprehension, challenging us to consider novel dimensions in our battle against drug resistance. As the narrative unfolds, the book takes you on a journey through the current state of research on drug resistance, providing a platform for the latest discoveries, methodologies, and innovative strategies. The chapters on novel approaches and future directions illuminate the path forward, offering a beacon of hope for researchers, clinicians, and students engaged in the quest for effective cancer therapies.

We hope this compilation serves as a valuable resource, fostering not only a deeper comprehension of drug resistance mechanisms but also inspiring the development of novel therapeutic paradigms. As we navigate the complicated landscape of cancer research, it is our collective hope that the insights contained herein contribute to the ongoing discussion and collaboration essential for conquering drug resistance and improving outcomes for individuals facing the challenges of cancer. Thank you for embarking on this intellectual journey with us. May the knowledge

shared within these pages propel us closer to the day when drug resistance in cancer becomes a conquerable adversary, paving the way for more effective and personalized treatment strategies.

Srinagar, Jammu and Kashmir, India Sameer Ullah Khan
Srinagar, Jammu and Kashmir, India Fayaz Malik

Acknowledgments

The creation of this book, *Drug Resistance in Cancer: Mechanisms and Strategies*, has been a collective effort, and we express our heartfelt gratitude to all those who have contributed to its realization.

First and foremost, we express our deepest appreciation to our parents, whose unwavering support and belief in our endeavors have been a constant source of inspiration. Your encouragement has been a guiding light, propelling us forward in the face of challenges. To our families, whose understanding and patience during the long hours of research and writing are deeply appreciated, we extend our heartfelt thanks. Your love and support have been the foundation upon which this project stands. We acknowledge the mentors and advisors who have shaped our academic journeys, providing guidance and wisdom that has enriched the content of this book. Your commitment to nurturing the next generation of researchers is invaluable. We extend our deepest appreciation to the esteemed authors whose scholarly insights and expertise have enriched the content of this volume. Your dedication to advancing the field of cancer research is evident in the depth and breadth of the chapters you have contributed. Our special acknowledgment goes to Shariqa Jan and Kaneez Fatima who were the major writing contributors to this book, their immense efforts make this book eminently more readable.

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Swiss/48/FM/2018-19 whose financial support has played a pivotal role in conducting the studies, acquiring essential resources, and facilitating the dissemination of knowledge.

Lastly, we thank the broader scientific community for its collaborative spirit. This book is a reflection of the collaborative efforts of many, and for that, we are truly grateful.

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About the Editors

Sameer Ullah Khan is currently a Post-Doctoral Fellow at The University of Texas, Genitourinary Medical Oncology—MD Anderson Cancer Center, USA. He has Ph.D. in Cancer Pharmacology (2022) at CSIR—Indian Institute of Integrative Medicine, India. His research interest is to decipher the role of cancer stem cells in aggressiveness and therapy resistance with a specialization in cancer metastasis, resistance, and drug discovery. He has been conferred with various prestigious awards, notably the Council of Scientific and Industrial Research—Junior Research Fellowship (JRF) and for Lectureship (LS)/Assistant Professor (CSIR-NET-JRF), CSIR-Senior research fellowship (SRF), The Graduate Aptitude Test in Life Science (GATE), The Indian Council of Medical Research (ICMR), and State Eligibility Test (J&K-SET) for Assistant Professor accredited by UGC (2014). He has actively participated in various international and national conferences as well as workshops. He has served as a referee for several international journals. He has more than 8 years of research experience in cancer pharmacology, molecular biology, drug discovery, epigenetics, and cell biology. He has also published more than 20 research as well as review articles in peer-reviewed international journals.

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Abbreviations

3-MA	3-Methyladenine
4-1BB	4-1BB ligand receptor (TNFRSF9)
4-OH-tamoxifen (4HT)	4-Hydroxytamoxifen
5-Aza-2′-deoxycytidine (DAC)	Decitabine
5-azadC	5-aza-2'-deoxycytidine
5-FU	5-Fluorouracil
ABC	ATP-binding cassette
ABCC6	ATP-binding cassette subfamily C member 6
ABL	Abelson murine leukemia viral oncogene homolog
ACT	Adoptive cell transfer
ADCC	Antibody-dependent cellular cytotoxicity
ADMA, SDMA	Asymmetric and symmetric dimethylarginine
AFP	Alpha-fetoprotein
AI	Artificial intelligence
AKT	Protein kinase B (Akt)
ALD	Alcoholic liver disease
ALDH	Aldehyde dehydrogenase
ALDH1A1	Aldehyde dehydrogenase 1A1
ALDH1A2	Aldehyde dehydrogenase 1 family member A2
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AMPK	AMP-activated protein kinase
APAF1	Apoptotic peptidase activating factor 1
APC	Adenomatous polyposis coli
APCs	Antigen-presenting cells
AR	Androgen receptor
AraC	Cytarabine
ATF4	Activating transcription factor 4
ATF6	Activating transcription factor 6
ATG14 L	Autophagy-related gene 14-like
ATG5-ATG12	Autophagy-related proteins 5 and 12
ATG6	Autophagy-related gene 6

ATGs	Autophagy-related genes
ATM	Ataxia telangiectasia mutated
ATP	Adenosine triphosphate
AURKB	Aurora kinase B
B cells	B lymphocytes
B7-H3	B7 homolog 3
BafA	Bafilomycin A1
Bak	BCL2 antagonist/killer
BATF3	Basic leucine zipper ATF-like transcription factor 3
Bax	Bcl-2-associated X protein
BC	Breast cancer
Bcl2	B-cell lymphoma 2
Bcl-2l10	BCL2-like 10
BCLAF1	Bcl2-associated transcription factor 1
Bcl-xl	B-cell lymphoma-extra-large
BCRP	Breast cancer resistance protein
BET	Bromodomain and extra-terminal domain
BFT	Bacteroides fragilis toxin
BH	Bcl-2-homology
BH3 mimetics	Bcl-2 homology 3 mimetics
BH3	Bcl-2 Homology 3
Bid	BH3 interacting domain death agonist
Bim	Bcl-2-like protein 11
BM	Bone marrow
BMDCs	Bone marrow-derived cells
Bmi-1	B-lymphoma Mo-MLV insertion region 1 homolog
BMI1	B-lymphoma Mo-MLV insertion region 1 homolog
BPTES	Bis-2-(5-phenyl acetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide
BRAF	B-raf proto-oncogene
BRCA	Breast cancer gene
BRCA1/BRCA2	Breast cancer gene 1/Breast cancer gene 2
BTZ	Bortezomib
C/EBP	CCAAT/Enhancer-binding protein
CA125	Cancer antigen 125
CAFs	Cancer-associated fibroblasts
CaM-Ks	Calmodulin-dependent kinases
CAR	Chimeric antigen receptor
Caspase	Cysteine-aspartic protease
CBP	CREB-binding protein
CCL1	C-C motif chemokine ligand 1
CCL20	CC Chemokine ligand 20

CCR2	Chemokine receptor 2
CD	Cluster of differentiation
CD4+	Cluster of differentiation 4 (a glycoprotein found on the surface of immune cells)
CD4+CD25+	Cluster of differentiation 4 and 25
CD44	Cluster of differentiation 44
CD73	Cluster of differentiation 73
CD8+	Cluster of differentiation 8 (a glycoprotein found on the surface of immune cells)
CD80	Cluster of differentiation 80
CD86	Cluster of differentiation 86
CDDP	Cisplatin
CDKN1C	Cyclin-dependent kinase inhibitor 1C
CDKs	Cyclin-dependent kinases
CDSS	Clinical decision support system
cFLIPL	Cellular FLICE-like inhibitory protein long form
CI	Complex I
CK1	Checkpoint kinase 1
CKDs	Chronic kidney diseases
CLIA	Clinical Laboratory Improvement Amendments
CML	Chronic myeloid leukemia
c-Myc	Myc proto-oncogene
CO2	Carbon dioxide
COL11A1	Collagen type XI alpha 1
COL4A2	Collagen type IV alpha 2 chain
COX-2	Cyclooxygenase-2
COX4I1, COX4I2	Cytochrome C oxidase subunit 4 isoforms 1 and 2
CPA	Cyclophosphamide
CpG	Cytosine-phosphate-guanine
CQ	Chloroquine
CRC	Colorectal carcinoma
CRISPR/Cas9	Clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9
CRKL	Crk-like protein
CRPC	Castration-resistant prostate cancer
CRS	Cytokine release syndrome
CSAs	Cancer-specific antigens
CSCs	Cancer stem cells
CSL	CBF-1, suppressor of hairless, lag-1 (transcription factor complex)
CT	Computed tomography
CTCs	Circulating tumor cells
CTF2	CCAAT-binding transcription factor 2

CTLA	Cytotoxic T-lymphocyte-associated protein
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CTLs	Cytotoxic T lymphocytes
CVDs	Cardiovascular diseases
CXCL12	C-X-C motif chemokine ligand 12
CXCR	Chemokine (C-X-C motif) receptor
CYP	Cytochrome P450
CYP1A1	Cytochrome P450 family 1 subfamily A member 1
CYP1B1	Cytochrome P450 family 1 subfamily B member 1
CYP24	Cytochrome P450 family 24 subfamily A member 1
CYP7B1	Cytochrome P450 family 7 subfamily B member 1
DAMP	Damage-associated molecular pattern
DCE MRI	Dynamic contrast-enhanced MRI
DCs	Dendritic cells
DDR	DNA damage response
DLL4	Notch ligand delta-like ligand 4
DNA	Deoxyribonucleic acid
DNAm	DNA methylation
DNAM-1	DNAX accessory molecule-1
DNA-PKcs	DNA-dependent protein kinase catalytic subunit
DNMTs	DNA methyltransferases
DOT1L	Disruptor of telomeric silencing 1-like
DOX	Doxorubicin
DR	Doxorubicin-resistant
DR	Drug resistance
DS	Doxorubicin-sensitive
DSBs	Double-strand breaks
DTP	Drug-tolerant persister
DUSP4	Dual specificity phosphatase 4
DWI MRI	Diffusion-weighted imaging MRI
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EGFR-TKIs	Epidermal growth factor receptor tyrosine kinase inhibitors
eIF2α	Eukaryotic initiation factor 2α
eIF2α	Eukaryotic translation initiation factor 2 alpha
ELOVL2	Elongation of very long chain fatty acids protein 2
EMT	Epithelial-mesenchymal transition
ENO1	Enolase 1
ENT1	Equilibrative nucleoside transporter 1

ENT2	Equilibrative nucleoside transporter 2
EpCAM	Epithelial cell adhesion molecule
EPI	Epirubicin
EPO	Erythropoietin
ER	Endoplasmic reticulum
ER	Estrogen receptor
ERBB2 (HER2)	Receptor tyrosine-protein kinase erbB-2 (Human epidermal growth factor receptor 2)
ERK/MAPK	Extracellular signal-regulated kinase/Mitogen-activated protein kinase
ERK1/2	Extracellular signal-regulated kinase 1/2
ERS	Endoplasmic reticulum stress
ERα	Estrogen receptor alpha
ESC	Embryonic stem cells
ESCC	Esophageal squamous cell carcinoma
ETC	Electron transport chain
EVs	Extracellular vesicles
EZH2	Enhancer of zeste homolog 2
FACS	Fluorescence-activated cell sorting
FAK	Focal adhesion kinase
FAO	Fatty acid oxidation
FAS	TNF receptor superfamily member 6
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FDG-PET	18 F-fluorodeoxyglucose positron emission tomography
FIP200	Focal adhesion kinase family interacting protein of 200 kDa
FLT3	FMS-like tyrosine kinase 3
FMT	Fecal microbiota transplantation
FOXO1	Forkhead box O1
Foxp3	Forkhead box P3
FZD6	Frizzled class receptor 6
Fzd8	Frizzled 8
G0	Resting phase in the cell cycle
G1	Initial growth phase in the cell cycle
G2	Growth phase in the cell cycle
G9a	Histone methyltransferase G9a
Gal-9	Galectin-9
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GAS-STING	cGAS-STING pathway
GBM	Glioblastoma multiforme
GBM	Glioblastoma multiforme
GCLC	Glutamate-cysteine ligase catalytic subunit
GCLC	Glutamate-cysteine ligase catalytic subunit

GCLP	Good Clinical Laboratory Practice
GDF15	Growth differentiation factor 15
GEMM	Genetically engineered mouse models
GITR	Glucocorticoid-induced TNFR-related protein
GLP	G9a-like protein
GLS	Glutaminase
GLUT	Glucose transporter
GPER	G protein-coupled estrogen receptor 1
GPR81	G-protein-coupled receptor 81
GREB1	Growth regulation by estrogen in breast cancer 1
GRP	Gefitinib-resistant cells
GRP78	Glucose-regulated protein 78
GSH	Glutathione
GSIs	Gamma-secretase inhibitors
GST	Glutathione S-transferase
GSTp	Glutathione S-transferase pi
H+-ATPase	Proton-ATPase
H2A.X	Histone 2A.X
H2AX	Histone 2AX
H2AX	Histone H2AX
H2AZ	Histone variant H2A.Z
H3K27	Histone 3 lysine 27
H3K27me3	Histone H3 lysine 27 trimethylation
H3K27me3	Trimethylation of histone 3 lysine 27
H3K36me3	Trimethylation of histone 3 lysine 36
H3K4Me3	Histone 3 lysine 4 trimethylation
H3K9	Histone 3 lysine 9
H3K9me1/2	Histone 3 lysine 9 mono/di-methylation
HATs	Histone acetyltransferases
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCQ	Hydroxychloroquine
HDAC1	Histone deacetylase 1
HDAC2	Histone deacetylase 2
HDACs	Histone deacetylases
HDR	Homology-directed repair
HDSCs	High-grade human glioma stem cells
HER2	Human epidermal growth factor receptor 2
HER3	Human epidermal growth factor receptor 3
HGF	Hepatocyte growth factor
HIAR	Hypoxia-induced angiogenesis regulator
HIC1	Hypermethylated in cancer 1
HIF-1α	Hypoxia-inducible factor 1-alpha
HIF-1α	Hypoxia-inducible factor 1-alpha

HK2	Hexokinase 2
HLA class Ia	Human leukocyte antigens class Ia
HLA	Human leukocyte antigen
HLA	Human leukocyte antigen
HMGB1	High-mobility group B1
HMGB1	High-mobility group box 1
hMLH1	Human MutL homolog 1
hMSCs	Human mesenchymal stem cells
HMTs	Histone methyltransferases
HMTs	Histone methyltransferases
HNF4	Hepatocyte nuclear factor 4
hnRNP	Heterogeneous nuclear ribonucleoprotein
HNSCC	Head and neck squamous cell carcinoma
HPMA	N-(2-hydroxypropyl) methacrylamide
HPV	Human papillomavirus
HR	Homologous recombination
hRFC	Human reduced folate carrier
HSP90	Heat shock protein 90
IAPs	Inhibitors of apoptosis proteins
IBD	Inflammatory bowel disease, hepatocellular carcinoma
IC50	Half-maximal inhibitory concentration
ICOS	Inducible T-cell CO-stimulator
ICs	Intracellular compartments
IDH	Isocitrate dehydrogenase
IDO1	Indoleamine 2,3-dioxygenase 1
IFN-γ	Interferon-gamma
IFN-γ	Interferon-gamma
IFP	Interstitial fluid pressure
IGF1	Insulin-like growth factor 1
IGF1R	Insulin-like growth factor 1 receptor
IL-10	Interleukin-10
IL-12	Interleukin-12
IL-13	Interleukin-13
IL-17	Interleukin-17
IL-23	Interleukin-23
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-6	Interleukin-6
ILK	Integrin-linked kinase
IMRT	Intensity-modulated radiation therapy
iPS	Induced pluripotent stem
IRE1α	Inositol-requiring enzyme 1 alpha
ISRIB	Integrated stress response inhibitor

ITIMs	Immunoreceptor tyrosine-based inhibitory motifs
JAK2/STAT5	Janus kinase 2/Signal transducer and activator of transcription 5
JNK	c-Jun N terminal kinase
KAT6A	Lysine acetyltransferase 6A
KDR	Kinase insert domain receptor
KIR	Killer cell immunoglobulin-like receptor
Kme1, Kme2, Kme3	Mono-, di-, and tri-methylation of lysine residues
KMTs	Lysine methyltransferases
KMTs	Lysine methyltransferases
LAG-3	Lymphocyte-activation gene 3
LAG-3	Lymphocyte-activation gene 3
LC3A/B	Microtubule-associated proteins 1A/1B light chain 3A/B
LDHA	Lactate dehydrogenase A
Lgr5	Leucine-rich repeat containing G protein-coupled receptor 5
LIR	Leukocyte immunoglobulin-like receptor
LMP	Lysosomal membrane permeabilization
LMP	Lysosomal membrane permeabilization
LMPs	Lysosomal membrane proteins
LncRNA	Long non-coding RNA
LPS	Lipopolysaccharide
LRP	Lung resistance-related protein
LRP6	Low-density lipoprotein receptor-related protein 6
M	Mitosis phase in the cell cycle
M1	Macrophage type 1
M1	Pro-inflammatory macrophages
M2	Anti-inflammatory macrophages
M2	Macrophage type 2
m6A	N6-methyladenosine
mAbs	Monoclonal antibodies
MACS	Magnetic-activated cell sorting
MAML	Mastermind-like (coactivator)
mBRCA1	Mutant BRCA1
MCAK	Mitotic centromere-associated kinesin
Mcl-1	Myeloid cell leukemia 1
MCT1	Monocarboxylate transporter 1
MDM2	Mouse double minute 2 homolog
MDR1	Multidrug resistance protein 1
MDSCs	Myeloid-derived suppressive cells
MEK	Mitogen-activated protein kinase kinase

MET	Mesenchymal-epithelial transition
MET	MET proto-oncogene
MGMT	O-6-methylguanine-DNA methyltransferase
MHC	Major histocompatibility complex
MHC-I	Major histocompatibility complex class I
MIM	Mitochondrial inner membrane
miR	MicroRNA
miR-129-5p	microRNA-129-5p
miR-137	microRNA-137
MK-0752	Gamma-secretase inhibitor used in targeting notch signaling
MKP2	MAPK phosphatase 2
MLH1	MutL homolog 1
MLL	Mixed-lineage leukemia
MM	Multiple myeloma
MMP9	Matrix metalloproteinase 9
MMPs	Matrix metalloproteinases
MOMP	Mitochondrial outer membrane permeabilization
MRI	Magnetic resonance imaging
MRP1	Multidrug resistance-associated protein 1
MRS	Magnetic resonance spectroscopy
MSC	Mesenchymal stem cell
MT	Metallothionein
MTD	Maximum tolerated dosage
mTOR	Mammalian target of rapamycin
mTORC1	Mechanistic target of rapamycin complex 1
mTORC2	Mechanistic target of rapamycin complex 2
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
mtTFA	Mitochondrial transcription factor A
Musashi-1	Musashi RNA binding protein 1
MVBs	Multivesicular bodies
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFLDs	Non-alcoholic fatty liver diseases
NAT1	N-acetyl transferase 1
NCR	Natural cytotoxicity receptor
NCT	ClinicalTrials.gov Identifier
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NF-κB	Nuclear factor-kappa B
NHEJ	Non-homologous end joining
NICD	Notch intracellular domain
NK	Natural killer
NKG2A	Natural killer group 2A

NKG2D	Natural killer group 2D
NMR	Nuclear magnetic resonance
NOD/SCID	Non-obese diabetic/Severe combined immunodeficiency
Noxa	Damage-regulated apoptosis modulator
Noxa	Phorbol-12-myristate-13-acetate-induced protein 1
NPC	Nuclear pore complex
NPs	Nanoparticles
NRF2	NFE2-related factor 2
NSCL	Non-small cell lung
NSCLC	Non-small cell lung cancer
OC	Ovarian cancers
OCCs	Ovarian carcinoma cell lines
Oct	Octamer-binding transcription factor
OCT1	Organic cation transporter 1
ODD	Oxygen-dependent degradation
OS	Overall survival
OXPHOS	Oxidative phosphorylation
p16INK4a	Cyclin-dependent kinase inhibitor 2A
p300	E1A binding protein P300
p38	p38 Mitogen-activated protein kinase
p53	Tumor protein 53
p62/SQSTM1	Sequestosome 1
PAI-1	Plasminogen activator inhibitor-1
PARP-1	Poly (ADP-ribose) polymerase-1
PD	Pharmacodynamic
PD-1/PD-L1	Programmed cell death protein 1/Programmed death-ligand 1
PDAC	Pancreatic ductal adenocarcinoma
PDGF beta	Platelet-derived growth factor beta
PDH	Pyruvate dehydrogenase
PDHK1	Pyruvate dehydrogenase kinase 1
PDIA1	Protein disulfide isomerase a1
PDK1	Phosphoinositide-dependent kinase-1
PDTC	Pyrrolidine dithiocarbamate
PDX	Patient-derived tumor xenografts
PEG-E2	Prostaglandin E2
PERK	Protein kinase RNA-like endoplasmic reticulum kinase
PFK1	Phosphofructokinase 1
PFKP	Phosphofructokinase 1 platelet
PFN1	Profilin1
PFS	Progression-free survival
PGM	Phosphoglucomutase

P-gp	P-glycoprotein
pH	Potential of hydrogen
PI3K/Akt	Phosphoinositide 3-kinase/Protein kinase B
PI3KC3	Class III phosphoinositide 3-kinase
PIK3CA	Phosphatidylinositol -4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetic
PKM2	Pyruvate kinase M2
PK-PD	Pharmacokinetic-pharmacodynamic
Pks	Polyketide synthases
PLGA	Poly(lactic-co-glycolic acid)
PMNs	Polymorphonuclear neutrophils
PORCN	Porcupine O-acyltransferase
PPO	Poly (propylene oxide)
PPP	Pentose phosphate pathway
PRI-724	Beta-catenin inhibitor
PRMT1-9	Protein arginine methyltransferases 1-9
PRMTs	Protein arginine methyltransferases
PRODH	Proline dehydrogenase
PSA	Prostate-specific antigen
PSCs	Pancreatic stellate cells
PSTI	Pancreatic secreted trypsin inhibitor
PTEN	Phosphatase and tensin homolog
PTGS2	Prostaglandin-endoperoxide synthase 2
PTK2	Protein tyrosine kinase 2
PTP	Protein tyrosine phosphatase
PTX	Paclitaxel
Puma	p53 upregulated modulator of apoptosis
RAF	Rapidly accelerated fibrosarcoma
RAS	Rat sarcoma
RECQL4	RecQ-like helicase 4
Rme1/MMA, Rme2	Mono- and di-methylation of arginine residues
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RP2D	Recommended phase 2 dose
RT	Radiation therapy
RTKs	Receptor tyrosine kinases
RT-PCR	Reverse transcription polymerase chain reaction
S	DNA replication phase in the cell cycle
SALL4	Sal-like protein 4
SAM	S-adenosyl-L-methionine
SASP	Senescence-associated secretory phenotype
SBRT	Stereotactic body radiation therapy
SCD1	Stearoyl-CoA desaturase 1
SCFAs	Short-chain fatty acids

SCLC	Small cell lung cancer
SCs	Stem cells
SDF-1 alpha	Stromal cell-derived factor 1 alpha
SDF-1	Stromal cell-derived factor-1
Sec62	Translocation protein SEC62
SETD2	SET domain containing 2
sgRNA	Single guide RNA
Shh	Sonic hedgehog
SILAC	Stable isotope labeling by amino acids in cell culture
siRNA	Small interfering RNA
siRNAs	Small interfering RNAs
SIRPα	Signal regulatory protein alpha
SLC19A1	Solute carrier family 19 member 1
SLC22A3	Solute carrier family 22 member 3
SMAR1	Scaffold/matrix-associated region 1
SMO	Smoothened
SMOC-2	SPARC-related modular calcium-binding protein 2
SMYD2	SET and MYND domain containing 2
SORE6	SOX2/Oct4 reporter element 6
SOX	SRY-related HMG-box
Sox2	Sex-determining region Y-box 2
SPT5	Transcription elongation factor SPT5
SRIB	Integrated stress response inhibitor
SSBs	Single-strand breaks
SSCs	Somatic stem cells
SSEA-1	Stage-specific embryonic antigen 1
SSP	Serine synthesis pathway
STAT3	Signal transducer and activator of transcription 3
STC1	Stanniocalcin 1
STF-31	A specific inhibitor of glucose transporter 1 (GLUT1)
SULT1A1	Sulfotransferase family 1A member 1
Suv39H1, Suv39H2	Suppressor of variegation 3-9 homolog 1 and 2
T cells	T lymphocytes
TAAs	Tumor-associated antigens
TAMs	Tumor-associated macrophages
TANs	Tumor-associated neutrophils
TATI	Tumor-associated trypsin inhibitor
TCA	Tricarboxylic acid
TFs	Transcription factors
TGF-β1	Transforming growth factor beta 1
Th17	T-helper 17 cells

Th2	T-helper 2
Th2	T-helper cell type 2
Thy-1	Thymocyte differentiation antigen-1
TIGAR	Tumor protein 53-induced glycolysis and apoptosis regulator
TIGIT	T cell immunoreceptor with Ig and ITIM domains
TILs	Tumor-infiltrating lymphocytes
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TIMPs	Tissue inhibitors of metalloproteinases
TKIs	Tyrosine kinase inhibitors
TME	Tumor microenvironment
TMZ	Temozolomide
TNBC	Triple-negative breast cancer
TNFRSF16	Tumor necrosis factor receptor superfamily member 16
TPP-Pluronic F127-hyaluronic acid nano micelles	Triphenylphosphonium-pluronic F127-hyaluronic acid nano micelles
TRA-1-60	Tumor-related antigen 1-60
TRAIL	TNF-related apoptosis-inducing ligand
Tregs	Regulatory T cells
TSACP	TruSeq amplicon—cancer panel
UbQ	Ubiquinone
ULBP	UL16-binding protein
ULK1	Unc-51 like autophagy activating kinase 1
uPAR	Urokinase plasminogen activator receptor
UPR	Unfolded protein response
USP22	Ubiquitin-specific peptidase 22
USP7	Ubiquitin-specific peptidase 7
Uvrag	UV radiation resistance-associated gene
VEGF	Vascular endothelial growth factor
VHL	von Hippel-Lindau
VPS	Vacuolar protein sorting
Vps38	Vacuolar protein sorting 38
Wnt	Wingless/integrated
XRCC1	X-ray repair cross-complementing protein 1
YB-1	Y-box binding protein-1
ZBP-89	Zinc binding protein 89
ZNF143	Zinc-finger factor 143
β-catenin	Beta-catenin

Introduction to Drug Resistance in Cancer

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Abstract

Treating cancer has so many hurdles, and drug resistance is one of them. Treatment strategies are evolving for cancer due to innate and acquired resistance capacity in them. The mechanism behind the resistance is constantly evolving in response to new drug treatment strategies and is an outcome of the acquired or adaptive mutation expression in cancer cells. In a broader perspective, cancer drug resistance can be governed by genetic, epigenetic, proteomic, metabolic, or microenvironment cues that ultimately enable selected resistant cancer cells to survive and progress under unfavorable conditions. Although the mechanism of drug resistance has been widely studied in cancer that progressively leads to the generation of new targets for novel anticancer drugs having better efficacy than previous ones. However, due to the high variability in resistance acquired by cancer cells toward existing drugs, novel strategic options with better efficacy

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need to be explored that overcome resistance. Combination therapy is a widely used alternative with a better success rate though the risk of amplified side effects is commonplace. However, recent groundbreaking immune therapy combination with the drugs is one of the ways to overcome drug resistance and has revolutionized anticancer therapy to a greater extent. However, more study is needed to be done at genetic, epigenetic, proteomic, and metabolic levels to identify targets of different cancers that can help to develop new therapies that are more effective to the existing challenge of cancer drug resistance. This chapter will focus on the recent challenges and strategies opted by cancer cells to withstand the current therapies at the molecular level.

Keywords

Drug resistance · Apoptosis · Cancer stem cells · Multi-drug resistance · Immune cells

1.1 Introduction

Presently, one of the challenging aspects of cancer biology is drug resistance in which cancer becomes forbearing to drug treatment, thus worsening the conditions of patients (Nikolaou et al. 2018; Saha and Sarkar 2021). Although initially various cancer types are sensitive to pharmaceutical therapy, over time, they acquire resistance and become more aggressive (Lu and Chao 2012; Michaelis et al. 2019; Mir et al. 2022a). Progress in discovering targeted therapy is advancing in recent years, which has led to the approval of various impactful anticancer drugs; nonetheless, resistance still shows a big hindrance to their success besides their life-threatening side effects (Oun et al. 2018; Tao et al. 2015). Cancer cells show evolving behavior of recurrence, dormancy, and drug resistance even after using conventional treatments like surgery, radiotherapy, and static chemotherapy, which in turn give birth to cancer stem cells (CSCs), thus producing a vicious cycle of resistivity and aggressiveness (Rajesh et al. 2017; Donnenberg and Donnenberg 2005). Advanced and more potent chemotherapeutic drugs have been able to succeed the previously available anticancer drugs individually, or they have been used chronologically or co-treated with prevailing treatments already available (Citron et al. 2003; Khan et al. 2022a). Moreover, altered chemotherapeutic dose intensity tactics like intermittent administration or higher doses along with supplements and growth factors to suppress the side effects on bone marrow have proved to be effective in preventing the regrowth of tumors (Citron et al. 2003; Hryniuk and Bush 1984; Sternberg et al. 2001). But clinically, cancer drug resistance remains a major hurdle in medical oncology, therefore understanding the acquired resistance mechanism and developing next-generation targeted therapies against these hallmarks are crucial to be taken at the earliest (Hanahan and Weinberg 2000, 2011; Fouad and Aanei 2017). With the advancement in the study of drug resistance massive efforts on the development of successful therapies against RTKs, nuclear, androgen, and Her2

receptors that potentially target oncogenes or other factors that lead to the transformation of cells (Wu and Fu 2018; Roviello et al. 2016; Martin et al. 2015; Fujita and Nonomura 2019; Asano et al. 2016; Barton et al. 2017; Niikura et al. 2016; Tolaney et al. 2020). Moreover, recent approaches of using immunological therapies were proven to be more successful in the recognition and destruction of cancer cells, for example, anti-CTLA and anti-PD-1/PD-L1 therapy remarkably show antitumor activity by dysfunctioning the negative regulators of the anticancer adaptive immune system, though the low chance of resistance remains the concern as that of conventional therapy (Leach et al. 1996; Iwai et al. 2002; Noguchi et al. 2017; Juneja et al. 2017; Ribas and Wolchok 2018). In cancer patients, drug resistance can be inherent due to evolving selection pressure or arise mostly under cancer therapy pressure (Zahreddine and Borden 2013). These resistant traits in cancer cells are achieved at genomic, epigenomic, and proteomic levels by following the Darwinian selection pressure rule (Álvarez-Arenas et al. 2019; Gerlinger and Swanton 2010; Theile and Wizgall 2021). With the advent of high-throughput assays, the idea of tumor heterogeneity came into existence, though there were already some hypothetical theories that supported this emerging idea. Tumor heterogeneity contributes to attaining resistance in which a few tumor cells divide and form a subpopulation of cells that may achieve features that enable them to become irresponsive to the particular drug over time (Jamal-Hanjani et al. 2015; Alizadeh et al. 2015; Roesch 2015). This process may sometimes emerge or initiate under selective drug pressure and play a vital role in resistance (Dexter and Leith 1986; Wu et al. 2017). Some contrasting features of sensitive cancer cells and drug-resistant cells are represented in Fig. 1.1.

In this chapter, we tried to discuss the spectrum of selective mechanisms displayed by cancerous cells to resist treatment including changes affecting drug chemistry, transporters, epigenetic changes, and amplification or modification of drug targets by accumulating protective mutations, which ultimately lead to impaired apoptosis (Fig. 1.2). Gaining these changes and genetic rewiring collectively leads to the clinically more difficult problem of multidrug resistance. Here,

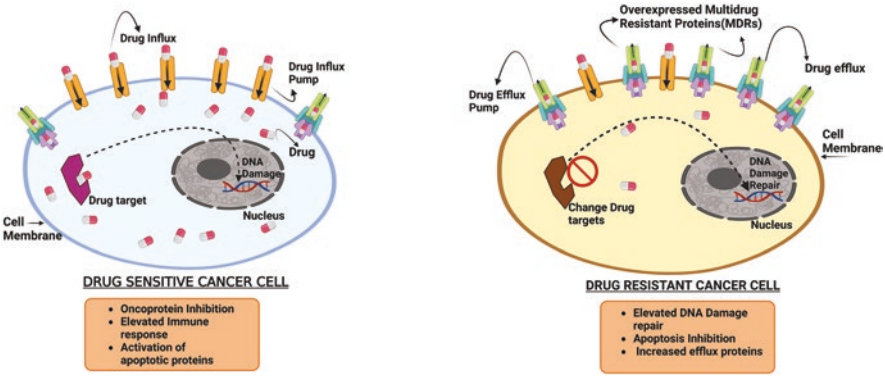

Fig. 1.1 The figure illustrates the key differences between drug-sensitive and drug-resistant cancer cells