

## A short update on cancer chemoresistance

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**Summary** Chemotherapeutic interventions in cancer patients are limited by the appearance of chemoresistance. For instance, advanced lung and ovarian cancer patients relapse invariably after few cycles of platinum-based chemotherapy. Disseminated tumors are characterized by genetic instability/heterogeneity, thus containing or generating a repertoire of resistant subpopulations. At the cellular level, altered drug uptake, efflux, and metabolization, as well as modifications of drug targets, increased repair, and decreased cell death complement the limited perfusion and adverse hypoxic/acidic extracellular conditions at the tumor level in retaining cancer cell viability. Similarly, targeted therapy is rendered ineffective by mutations of the specific target protein within a few months or years of administration. Assessment of the expression profiles of resistant tumor cells revealed extensive changes in numerous pathways affecting hundreds of genes. Therefore, reversal of drug resistance will require individual profiles of drug resistance mediators and the combination of several specific drugs, targeting critical components to provide new therapeutic options.

**Keywords** Chemoresistance · Cancer stem cells · Targeted therapy · Apoptosis

### Chemoresistenz bei Tumorerkrankungen – eine aktuelle Übersicht

**Zusammenfassung** Die Chemotherapie wird in Krebspatienten durch das Auftreten von Chemoresistenz

begrenzt. Zum Beispiel rezidivieren Lungen- und Ovarialkarzinompatienten schon nach wenigen Zyklen der platinbasierten Chemotherapie. Disseminierte Tumoren weisen genetische Instabilität/Heterogenität auf und enthalten oder generieren resistente Subpopulationen. Auf der Zellebene komplementieren veränderte Wirkstoffaufnahme, -efflux und -metabolisierung, Modifikationen der Zielproteine, gesteigerte Reparaturprozesse und verminderter Zelltod die herabgesetzte Perfusion und die ungünstigen hypoxischen/azidotischen Bedingungen auf Tumorebene, die die Viabilität der Tumorzellen erhalten. In ähnlicher Weise wird bei der zielgerichteten Chemotherapie die Wirksamkeit durch Mutationen des Zielproteins innerhalb weniger Monate oder Jahre herabgesetzt. Eine Erfassung der Expressionsprofile resistenter Tumorzellen zeigen Änderungen in zahlreichen Stoffwechselwegen die hunderte Gene betreffen. Folglich verlangt die erfolgreiche Reversion der Resistenz die Erfassung individueller Profile der verantwortlichen Mediatoren und den Einsatz einer Kombination von Wirkstoffen gegen kritische Zielproteine.

**Schlüsselwörter** Chemoresistenz · Tumorstammzellen · Zielgerichtete Therapie · Apoptose

### Introduction

Disseminated cancer is treated with systemic chemotherapy, which is limited by toxic side effects and eventually by emergence of chemoresistance [1]. The so-called primary resistance is already present before therapy, and, in contrast, acquired resistance develops as tumor adaption during treatment cycles [2–4]. Alterations frequently associated with chemoresistance comprise changes in drug transport and metabolism, modification of drug targets, as well as an elevated threshold to initiate cell death. The genetic instability of cancer cells results in

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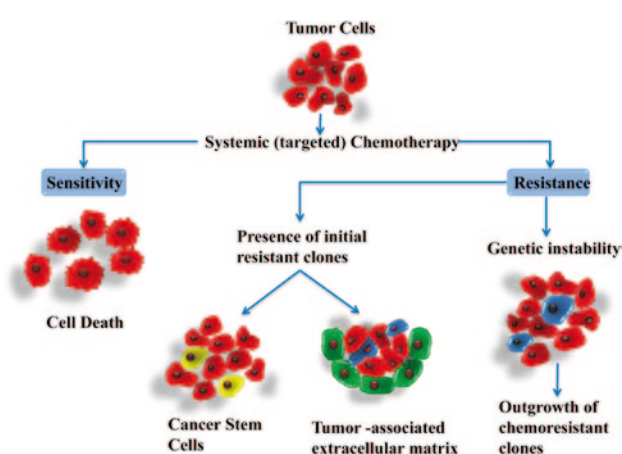
the generation of a range of heterogenous clones, which under therapeutic pressure leads to the expansion of the most chemoresistant subpopulations, thus driving tumor relapse. Aggravating the situation, resistance to one particular drug may result in diverse cellular changes that impair the efficacy of a whole range of chemotherapeutics, a phenomenon designated multidrug resistance (MDR). The majority of patients with disseminated disease undergoing systemic therapy will feature resistance and tumor progression. Additionally, primary resistance has been recognized in nearly half of all cancer patients, and early appearance of disease progression is almost invariably found in lung and ovarian cancer following platinum-based chemotherapy [5–8].

## Mechanisms of drug resistance

### Types of chemoresistance and drug disposition

Appearance of resistant tumor cells may follow different cellular pathways. Primary resistance is based on the initial presence of spontaneous resistant tumor cell clones that remain after deletion of the chemosensitive subpopulations and reconstitute the clinical observable lesions (Fig. 1). Whether these resistant clones have stem-like characteristics or random possession of different cellular characteristics or survive under special surroundings (niches) in a protected dormant stage is the focus of ongoing research [9]. Acquired resistance consists of stochastic events in the individual cancer cells predisposing for cell survival, generation of minimal residual disease, and clinical recurrence [1, 10, 11].

A primary mode of resistance comprises drug metabolism, covering cellular uptake, and extrusion as well as



**Fig. 1** Schematic representation of the possible effects of chemotherapy on tumor cells. Sensitive cancer cells commit cell death and resistant cells survive through several possible mechanism: **a** as resistant, preexisting cancer stem cells, **b** as normal or cancer stem cells protected through interaction with extracellular matrix in niches, or **c** as cells randomly acquiring resistant phenotypes in the course of genetic instability and generation of heterogenous tumor subpopulations

**Table 1** Most important mechanisms of chemoresistance at the cellular and tumor physiological level

<i>Cellular Mechanisms of chemoresistance</i>
Decreased drug uptake
Alterations to drug metabolism
Increased drug efflux
Modification of the drug targets
Enhanced DNA repair
Inactivation of apoptotic proteins
Activation of anti-apoptotic proteins, among others
<i>Tumor physiological mechanisms of chemoresistance</i>
Intermittent and irregular perfusion
Limited drug diffusion
Hypoxia
Acidic environment
Adhesion-mediated resistance

intracellular derivatization (Table 1). In general, hydrophobic compounds such as taxanes and camptothecins can pass the cell membrane freely, whereas other drugs depend on facilitated uptake by transporters or exert their activity at extracellular binding sites [10]. Resistance could be effected in the latter case by decreased expression or shedding of the cell surface receptor and mutations of the binding site. Alterations of nucleoside or folate transporters result in impaired uptake of nucleoside drugs, such as cytarabine and methotrexate, respectively [12–14].

### Drug transport

The so-called P-glycoprotein (P-gp) was the first member of the ATP-binding cassette (ABC) class of membrane transporters, actively extruding xenobiotics from cell interior [10]. As these transporters display a broad substrate specificity, they confer chemoresistance to a whole panel of unrelated drugs, a characteristic designated MDR. In contrast, atypical MDR stems from alterations in topoisomerase II, causing MDR to anthracyclines, podophyllotoxins, and other drugs [15]. Of the 48 known ABC transporters in humans, P-gp (ABCB1) transports a wide variety of hydrophobic anticancer drugs such as vinblastine, doxorubicin, vincristine, and taxol, among others, and the MDR-associated protein 1 (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2) transport various other chemotherapeutics [10].

An important feature of drug resistance is that development of resistance to one drug can lead to resistance to other drugs [11, 16]. In particular, MRP1 transports negatively charged compounds and drugs that became derivatized by glutathione (GSH), glucuronic acid, or sulfate [17–19], and BCRP participates in chemoresistance to topotecan, anthracyclines, and mitoxantrone [10]. Other transporters, such as MDR-associated protein 2 (MRP2) also called canalicular multispecific organic

anion transporter 1 (cMOAT) or ABCC2, are expressed in normal liver tissue and affect chemoresistance indirectly by altering the elimination of chemotherapeutics [20]. Eventually, coadministration of chemotherapeutics and MDR inhibitors like verapamil, cyclosporine, and next-generation specific inhibitors was not successful in reversing clinical drug resistance due to the manifold other resistance mechanisms coexpressed [21, 22].

Recently, other families of membrane transporters, such as organic anion transport proteins (OATPs), were implicated in the uptake and extrusion of chemotherapeutics [23, 24]. OATPs are multispecific transport proteins, which means that they can transport a wide range of structurally unrelated compounds. In particular, OATPs 1B1 and 1B3 were demonstrated to be involved in paclitaxel transport in ovarian cancer cell lines [25]. OATPs has been implicated in transport of the camptothecin analogs, SN-38, flavopiridol, methotrexate, the taxanes paclitaxel and docetaxel, as well as imatinib (Gleevec®) [26].

### Drug metabolism

A range of anticancer drugs exist as inactive prodrugs that have to be metabolically activated. For example, modified nucleosides such as cytarabine (AraC) require intracellular phosphorylation to yield the active triphosphate form, and the camptothecin irinotecan (CPT-11) is activated by carboxyesterases to its pharmacologic active metabolite SN-38. To decrease the efficacy of these drugs, cancer cells develop resistance through downregulation or mutation of the enzymes for metabolic activation, such as deoxycytidine kinase in the case of cytarabine and carboxyesterases for irinotecan [27–29]. Additionally, metabolic inactivation in the liver influences the pharmacokinetics of the active drugs [30].

Cells try to get rid of cytotoxic drugs via metabolic inactivation, employing protein binding, conjugation, and oxidation/reduction [1]. Platinum complexes are coupled to GSH and eliminated by ABC transporter-mediated efflux [31]. Members of the metallothionein family, small cysteine-rich proteins, bind and inactivate metals. The anticancer activity of resveratrol against breast cancer cells is reduced by sulfation, and the corresponding enzymes, namely sulfotransferases, are differently expressed in malignant breast tissues [32, 33]. Drugs, such as irinotecan, which is used for colon cancer treatment, are inactivated via phase I drug-metabolizing enzymes, CYP450 [34, 35]. Overexpression of CYP3A4 was found in a colon cancer cell line enriched for putative cancer stem cells [36].

### Targeting of oncogenes

Instead of a relatively unspecific systemic chemotherapy, targeted therapy tries to specifically hit oncogenes that drive the growth of malignant tissues [37]. Most promi-

nent examples of targeted therapy comprise imatinib directed to the BCR/ABL tyrosine kinase in leukemia, gefitinib and erlotinib against the epidermal growth factor receptor (EGFR) tyrosine kinase, trastuzumab targeting human epidermal growth factor (HER-2) in breast cancer, and crizotinib directed to the ALK kinase, among others in clinical use or under development [38–40]. Targeted therapies eliminate tumor cells and have fewer side effects, but under therapy, cells evade the pressure by mutating the target within a few months or years or show outgrowth of small resistant subpopulations present prior to treatment [41, 42]. Characterization of the mutations of the target proteins by sequence analysis and molecular modeling of the alterations is used to generate active second-generation targeted drugs [43, 44]. Additionally, cells have backup systems consisting of alternative parallel pathway supporting tumor survival and activation of alternative routes leaving the targeted approach ineffective [45]. In the case of successful tumor cell kill due to inhibition of both the original and alternative pathways, this constitutes a synthetic lethal relationship that may be exploited clinically [46]. One example is seen in breast and ovarian cancers carrying mutations in the *BRCA1* and *BRCA2* (breast cancer 1/2) genes, which are killed by targeting poly (ADP-ribose) polymerase (PARP) protein with specific inhibitors [47, 48].

### Resistance to induction of apoptosis

Eventually, the fate of the cells is determined by its threshold to commit programmed cell death after irreparable damage to essential components. This type of chemoresistance results from downregulation/mutation of proapoptotic proteins, such as p53, Bak, Bax, SMAC/DIABOLO, and phosphatase and tensin homolog (PTEN), among others, or activation of prosurvival proteins, such as B cell lymphoma 2 (Bcl-2), inhibitors of apoptosis (IAPs), PI3K/Akt, and others [49]. Cyclosporine-binding proteins, the cyclophilin family, seems to be involved in the suppression of the apoptotic cascade in selected cancer cell types [50, 51]. Almost 50 % of tumors express mutated p53, which makes the cells less prone to initiation of apoptosis and induction of cell death after DNA damage [1]. In particular, prostate, lung, and ovarian cancer cells become highly resistant to any type of chemotherapy after failure of the first-line therapies, most likely to high resistance to induce cell death [8].

### Tumor physiological mechanisms of resistance

Solid tumors exhibit irregular vascularization associated with intermittent perfusion and hypoxic conditions. As tumor cells switch to glycolysis, lactate accumulates in the interstitial space, and the resulting acidic condition in conjunction with high interstitial pressure impedes efficacy and diffusion of drugs significantly [8]. Cancer stem cells most likely survive in hypoxic and less per-

fused bone marrow niches in a dormant state [9]. Thus, the cellular mechanisms of chemoresistance are amplified at the tumor “organ” level.

## Conclusion

Chemoresistance limits the survival of advanced cancer patients receiving chemotherapy. Pre-existing or induced resistant clones are present within the highly heterogeneous tumor cell mass and trigger tumor relapses following treatment cycles solely eliminating the chemosensitive mass of cells [52, 53]. In contrast to the previous view of single or restricted cellular alterations to achieve resistance, gene expression analysis revealed the complex changes occurring in resistant variants, affecting a host of different pathways. For instance, changes in solute carrier family 31, member 1/copper transporter (SLC31A1), ABCC2 (MRP2), and copper-transporting ATPases 1/2 (ATP7A/B) modulate influx/efflux of cisplatin; mutS homolog 6 mismatch repair protein (MSH6), MutL homolog 1 DNA repair protein (MLH1), X-ray repair cross-complementing protein 1 (XRCC1), excision repair cross-complementation group 1/2 proteins (ERCC1/2), and DNA repair protein complementing XP-A cells (XPA) are responsible for increased DNA repair; myeloperoxidase (MPO), superoxide dismutase 1 (SOD1), GSH S-transferase  $\mu$ 1 (GSTM1), GSH S-transferase  $\pi$ 1 (GSTP1), and metallothioneins impede the cytotoxic effects of cisplatin; and DNA polymerases POLH/B provide tolerance to DNA-directed drugs in conjunction with a host of other modified pathways [54]. Therefore, successful reversal of chemoresistance would require detailed knowledge of the individual causes of its molecular basis and specific targeting of critical components contributing to drug inactivation. Whether elimination of a small cancer stem cell population feeding the tumor will prove to be effective remains to be investigated [9, 55, 56].

## Conflict of interest

The authors declare to have no conflict of interest.

## References

- Wilson TR, Longley DB, Johnston PG. Chemoresistance in solid tumours. *Ann Oncol*. 2006;17:315–24.
- Meads MB, Gatenby RA, Dalton WS. Environment-mediated drug resistance: a major contributor to minimal residual disease. *Nat Rev Cancer*. 2009;9:665–74.
- Lippert TH, Ruoff HJ, Volm M. Current status of methods to assess cancer drug resistance. *Int J Med Sci*. 2011;8:245–53.
- Zahreddine H, Borden LB. Mechanisms and insights into drug resistance in cancer. *Front Pharmacol*. 2013;4:28.
- Pinedo HM, Giaccone G. Drug resistance in the treatment of cancer. Cambridge: Cambridge University Press; 2007.
- Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. *Lancet*. 2014. pii: S0140-6736(13)62146-7.
- Rosell R, Cecere F, Santarpia M, Reguart N, Taron M. Predicting the outcome of chemotherapy for lung cancer. *Curr Opin Pharmacol*. 2006;6:323–31.
- Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. *Nat Rev Cancer*. 2013;13:714–26.
- O'Connor ML, Xiang D, Shigdar S, Macdonald J, Li Y, Wang T, Pu C, Wang Z, Qiao L, Duan W. Cancer stem cells: a contentious hypothesis now moving forward. *Cancer Lett*. 2014;344:180–7.
- Gottesman MM. Mechanisms of cancer drug resistance. *Annu Rev Med*. 2002;53:615–27.
- Ullah MF. Cancer multidrug resistance (MDR): a major impediment to effective chemotherapy. *Asian Pac J Cancer Prev*. 2008;9:1–6.
- Galmarini CM, Mackey JR, Dumontet C. Nucleoside analogues: mechanisms of drug resistance and reversal strategies. *Leukemia*. 2001;15:875–90.
- Damaraju VL, Damaraju S, Young JD, Baldwin SA, Mackey J, Sawyer MB, et al. Nucleoside anticancer drugs: the role of nucleoside transporters in resistance to cancer chemotherapy. *Oncogene*. 2003;22:7524–36.
- Longo-Sorbello GS, Bertino JR. Current understanding of methotrexate pharmacology and efficacy in acute leukemias. Use of newer antifolates in clinical trials. *Haematologica*. 2001;86:121–7.
- Nooter K, Stoter G. Molecular mechanisms of multidrug resistance in cancer chemotherapy. *Pathol Res Pract*. 1996;192:768–80.
- Nobili S, Landini I, Mazzei T, Mini E. Overcoming tumor multidrug resistance using drugs able to evade P-glycoprotein or to exploit its expression. *Med Res Rev*. 2012;32:1220–62.
- Jedlitschky G, Leier I, Buchholz U, Barnouin K, Kurz G, Keppler D. Transport of glutathione, glucuronate, and sulfate conjugates by the MRP gene-encoded conjugate export pump. *Cancer Res*. 1996;56:988–94.
- Konig J, Nies AT, Cui Y, Leier I, Keppler D. Conjugate export pumps of the multidrug resistance protein (MRP) family: localization, substrate specificity, and MRP2-mediated drug resistance. *Biochim Biophys Acta*. 1999;1461:377–94.
- Borst P, Evers R, Kool M, Wijnholds J. A family of drug transporters: the multidrug resistance-associated proteins. *J Natl Cancer Inst*. 2000;92:1295–302.
- Jäger W, Gehring E, Hagenauer B, Aust S, Senderowicz A, Thalhammer T. The role of hepatic Mrp2 in the interaction of flavopiridol and bilirubin: impact on therapy. *Int J Clin Pharmacol Ther*. 2003;41:610–1.
- Haberl I, Swatonek H, Schaufler K, Ulsperger E, Wenzl E, Theyer G, Hamilton G, Thalhammer T. P-glycoprotein-mediated multidrug resistance is modulated by pretreatment with chemosensitizers in HCT-8 carcinoma cells in vitro. *Int J Oncol*. 1998;12:1137–42.
- Binkhathlan Z, Lavasanifar A. P-glycoprotein inhibition as a therapeutic approach for overcoming multidrug resistance in cancer: current status and future perspectives. *Curr Cancer Drug Targets*. 2013;13:326–46.
- Svoboda M, Riha J, Wlcek K, Jaeger W, Thalhammer T. Organic anion transporting polypeptides (OATPs): regulation of expression and function. *Curr Drug Metab*. 2011;12:139–53.
- Buxhofer-Ausch V, Secky L, Wlcek K, Svoboda M, Kounnis V, Briasoulis E, Tzakos AG, Jaeger W, Thalhammer T. Tumor-specific expression of organic anion-transporting polypeptides: transporters as novel targets for cancer therapy. *J Drug Deliv*. 2013;2013:863539.

25. Svoboda M, Wlcek K, Taferner B, Hering S, Stieger B, Tong D, Zeillinger R, Thalhammer T, Jäger W. Expression of organic anion-transporting polypeptides 1B1 and 1B3 in ovarian cancer cells: relevance for paclitaxel transport. *Biomed Pharmacother.* 2011;65:417–26.
26. Obaidat A, Roth M, Hagenbuch B. The expression and function of organic anion transporting polypeptides in normal tissues and in cancer. *Annu Rev Pharmacol Toxicol.* 2012;52:135–51.
27. Sampath D, Cortes J, Estrov Z, Du M, Shi Z, Andreeff M, et al. Pharmacodynamics of cytarabine alone and in combination with 7-hydroxystaurosporine (UCN-01) in AML blasts in vitro and during a clinical trial. *Blood.* 2006;107:2517–24.
28. Xu Y, Villalona-Calero MA. Irinotecan: mechanisms of tumor resistance and novel strategies for modulating its activity. *Ann Oncol.* 2002;13:1841–51.
29. Bardenheuer W, Lehmborg K, Rattmann I, Brueckner A, Schneider A, Sorg UR, et al. Resistance to cytarabine and gemcitabine and in vitro selection of transduced cells after retroviral expression of cytidine deaminase in human hematopoietic progenitor cells. *Leukemia.* 2005;19:2281–8.
30. Platzer P, Thalhammer T, Hamilton G, Ulsperger E, Rosenberg E, Wissiack R, Jäger W. Metabolism of camptothecin, a potent topoisomerase I inhibitor, in the isolated perfused rat liver. *Cancer Chemother Pharmacol.* 2000;45:50–4.
31. Meijer C, Mulder NH, Timmer-Bosscha H, Sluiter WJ, Meersma GJ, De Vries EG. Relationship of cellular glutathione to the cytotoxicity and resistance of seven platinum compounds. *Cancer Res.* 1992;52:6885–9.
32. Miksits M, Wlcek K, Svoboda M, Kunert O, Haslinger E, Thalhammer T, Szekeres T, Jäger W. Antitumor activity of resveratrol and its sulfated metabolites against human breast cancer cells. *Planta Med.* 2009;75:1227–30.
33. Aust S, Obrist P, Klimpfing M, Tucek G, Jäger W, Thalhammer T. Altered expression of the hormone- and xenobiotic-metabolizing sulfotransferase enzymes 1A2 and 1C1 in malignant breast tissue. *Int J Oncol.* 2005;26:1079–85.
34. Kelley SL, Basu A, Teicher BA, Hacker MP, Hamer DH, Lazo JS. Overexpression of metallothionein confers resistance to anticancer drugs. *Science.* 1988;241:1813–5.
35. Xu Y, Villalona-Calero MA. Irinotecan: mechanisms of tumor resistance and novel strategies for modulating its activity. *Ann Oncol.* 2002;13:1841–51.
36. Olszewski U, Liedauer R, Ausch C, Thalhammer T, Hamilton G. Overexpression of CYP3A4 in a COLO 205 colon cancer stem cell model in vitro. *Cancers (Basel).* 2011;3:1467–79.
37. Weinstein IB. Cancer. Addiction to oncogenes—the Achilles heel of cancer. *Science.* 2002;297:63–4.
38. Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med.* 2003;349:1423–32.
39. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* 2004;350:2129–39.
40. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* 2005;353:123–32.
41. Hofmann WK, Komor M, Wassmann B, Jones LC, Gschaidmeier H, Hoelzer D, et al. Presence of the BCR-ABL mutation Glu255Lys prior to STI571 (imatinib) treatment in patients with Ph+ acute lymphoblastic leukemia. *Blood.* 2003;102:659–61.
42. Inukai M, Toyooka S, Ito S, Asano H, Ichihara S, Soh J, et al. Presence of epidermal growth factor receptor gene T790M mutation as a minor clone in non-small cell lung cancer. *Cancer Res.* 2006;66:7854–8.
43. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science.* 2001;293:876–80.
44. Blencke S, Ullrich A, Daub H. Mutation of threonine 766 in the epidermal growth factor receptor reveals a hotspot for resistance formation against selective tyrosine kinase inhibitors. *J Biol Chem.* 2003;278:15435–40.
45. le Coutre P, Tassi E, Varella-Garcia M, Barni R, Mologni L, Cabrita G, et al. Induction of resistance to the Abelson inhibitor STI571 in human leukemic cells through gene amplification. *Blood.* 2000;95:1758–66.
46. Nijman SM. Synthetic lethality: general principles, utility and detection using genetic screens in human cells. *FEBS Lett.* 2011;585:1–6.
47. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature.* 2005;434:913–7.
48. Montoni A, Robu M, Pouliot E, Shah GM. Resistance to PARP-inhibitors in cancer therapy. *Front Pharmacol.* 2013;4:18.
49. Fodale V, Pierobon M, Liotta L, Petricoin E. Mechanism of cell adaptation: when and how do cancer cells develop chemoresistance? *Cancer J.* 2011;17:89–95.
50. Thalhammer T, Kieffer LJ, Jiang T, Handschumacher RE. Isolation and partial characterization of membrane-associated cyclophilin and a related 22-kDa glycoprotein. *Eur J Biochem.* 1992;206:31–7.
51. Hamilton G. Cyclophilin A as a target of Cisplatin chemosensitizers. *Curr Cancer Drug Targets.* 2014;14:46–58.
52. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144:646–74.
53. Marusyk A, Polyak K. Tumor heterogeneity: causes and consequences. *Biochim Biophys Acta.* 2010;1805:105–17.
54. Lu HP, Chao CC. Cancer cells acquire resistance to anticancer drugs: an update. *Biomed J.* 2012;35:464–72.
55. Hamilton G, Olszewski U. Chemotherapy-induced enrichment of cancer stem cells in lung cancer. *J Bioanal Biomed.* 2013;S9:003.
56. Castells M, Thibault B, Delord JP, Couderc B. Implication of tumor microenvironment in chemoresistance: tumor-associated stromal cells protect tumor cells from cell death. *Int J Mol Sci.* 2012;13:9545–71.