scientific reports

Check for updates

OPEN

EDITORIAL

Therapeutic resistance and combination therapy for cancer: recent developments and future directions

Chendil Damodaran[1], Je-Yoel Cho[2] & Cenap Güngör[3]✉

The diverse and heterogeneous nature of cancer is a fundamental characteristic that is responsible for therapy resistance, progression, and recurrence of disease. In order to enhance therapeutic efficacy, novel combination therapies are currently being proposed and utilized in clinical practice to effectively manage or retard disease progression. Several factors contribute to therapeutic resistance, including elevated expression of survival factors, mutations in genes that limit therapeutic effectiveness, multidrug resistance, and the potential involvement of cancer stem cells. This *Scientific Reports* Collection covers the underlying mechanisms responsible for therapeutic resistance. Additionally, the publications from this Collection highlight numerous innovative molecules to overcome this resistance and significantly sensitize tumors across various cancer models.

Targeted therapies in cancer treatment have emerged as a promising alternative to conventional methods such as surgery, chemotherapy, and radiation, which are often criticized for their associated toxicity and the potential for disease recurrence[1]. Imatinib has shown efficacy in treating chronic myelogenous leukemia[2], while other targeted therapies have been developed for lung[3,4] and breast cancers[5,6]. Combining targeted therapies with standard treatments has inspired the fight against cancer.

Immunotherapies have also garnered substantial attention in recent years, as they fundamentally transform the cancer treatment landscape and counteract cancer cells by leveraging and activating the immune response against tumors. This process of boosting innate and/or adaptive immune responses through immunomodulation[7] is a new powerful therapeutic tool.

Combination therapies, with their potential to reduce the number of drugs needed for tumor regression while launching a multifaceted assault to combat therapeutic resistance and prevent tumor recurrence, present additional therapeutic advantages over monotherapies. More than twenty anticancer combination therapies have received FDA approval, and several clinical trials are currently exploring the therapeutic potential of combination strategies. This promising approach, which offers practical benefits and therapeutic advantages, is a key area of interest in the fight against cancer.

Given its emerging importance, the intercellular transfer of therapeutic resistance warrants deeper investigation in future studies. Although cisplatin-based chemotherapy is commonly employed to treat advanced cancers, the development of resistance remains a significant challenge, with its underlying mechanisms not yet fully elucidated. Emerging evidence suggests that the exosomal transfer of microRNAs (miRNAs) within the tumor microenvironment (TME) plays a crucial role in conferring cisplatin (DDP) resistance. For instance, miR-21 derived from M2-polarized tumor-associated macrophages has been shown to promote DDP resistance in gastric cancer cells by suppressing apoptosis and enhancing PI3K/AKT signaling by downregulating PTEN. Similarly, exosomes derived from cancer-associated fibroblasts (CAFs) can confer cisplatin resistance in NSCLC cells by transferring miR-130a[8]. The packaging of miR-130a into exosomes is mediated by the RNA-binding protein PUM2, suggesting that CAF-derived exosomal miR-130a may be a potential therapeutic target

[1]Department of Pharmaceutical Science, College of Pharmacy, Texas A&M University, College Station, TX, USA. [2]Department of Biochemistry, College of Veterinary Medicine, Research Institute for Veterinary Science, and BK21 FOUR Future Veterinary Medicine Leading Education and Research Center, Comparative Medicine Disease Research Center (CDRC), Seoul National University, Seoul 08826, Republic of Korea. [3]Department of General, Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ✉email: c.guengoer@uke.de

to overcome cisplatin resistance in NSCLC[9]. These findings highlight the therapeutic potential of targeting exosome-mediated intercellular communication in the TME to overcome chemotherapy resistance in cancer.

In this Collection, the authors present novel molecules and outline potential mechanisms of action in various preclinical cancer models. Their compelling results could significantly impact and advance our understanding of cancer treatment, potentially leading to transformative changes in clinical settings.

Collection overview

Biegala et al[10] demonstrated that reversing BRCA2 mutations enhances therapeutic efficacy of PARP inhibitors (PARPi) in ovarian cancer. The study emphasized the involvement of DNA damage pathways on the therapeutic effects of olaparib, as increased expression of the homologous recombination repair pathway can inhibit its function[11,12] by upregulating BRCA1/2[13]. Moreover, inhibiting ATR function—either genetically using siRNA-ATR or pharmacologically with ceralasertib—and inhibiting CHK1 (via MK8776 or siCHK1) significantly improved the efficacy of treatments for ovarian cancer cells harboring BRCA2 mutations.

Targeting epidermal growth factor receptor (EGFR) is considered one of the most effective strategies for treating non-small cell lung cancer (NSCLC), as 10–15% of patients exhibit activation of this pathway [14]. Several EGFR tyrosine kinase inhibitors (TKIs), including afatinib and dacomitinib, initially demonstrate promising efficacy; however, resistance often develops over time due to mutations in the catalytic domain of EGFR (T790M)[15]. Osimertinib, an EGFR mutant TKI, is the first-line treatment choice[16]. Although patients may show initial responsiveness, many ultimately develop resistance. La Monica et al.[17] demonstrated that increased glucosylceramides, downstream effectors of ceramide signaling, may contribute to this resistance. Intratumoral injection of the pharmacological inhibitor 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) sensitized osimertinib-resistant NSCLC models in preclinical studies.

Triple-negative breast cancer (TNBC) occurs in ~ 15–20% of breast cancer patients[18], and despite some positive results with PARPi[19] or anti-EGFR/TROP2 therapies[20,21], virtually all women with TNBC ultimately succumb to metastatic disease[22–24]. To overcome intrinsic resistance, Martin et al.[25] identified increased expression of aryl hydrocarbon receptor (AhR) as a negative regulator of STImulator of Interferon Genes (STING) expression[26,27], which in turn downregulates IFN-1. The study further demonstrated that PARPi activates AhR signaling, which causes resistance in BRAC1-deficient TNBC cells; hence, combining AhR antagonist (BAY) and PARPi (TAL) synergistically enhances therapeutic efficacy by upregulating IFN-1 production and potentiates PARPi function in BRAC1-negative TNBC cells.

The chemoresistance of TNBC cells to paclitaxel was investigated by Calistri et al[28] using single-cell RNA sequencing (scRNA-seq). Their findings revealed that the concurrent induction of innate immune responses by IFNB and IFNG, combined with the downregulation of cell-cycle checkpoint proteins, enables TNBC cells to proliferate. Further studies identified the involvement of three key transcription factors, FOSL1, NFE2L2, and ELF3, which may play critical roles in proliferation and contribute to paclitaxel resistance in TNBC cells. While the role of ELF3 in proliferation, survival, and metastasis is well established in various cancer types[29,30], the present study demonstrated that knocking down ELF3 expression caused the cells to arrest at the G1 phase of the cell-cycle and resulted in growth inhibition, thereby enhancing paclitaxel efficacy in TNBC cell lines. Thus, ELF3 expression may predict potential paclitaxel resistance in TNBC cells, and inhibiting ELF3 could amplify the effect of paclitaxel.

Cancer immunotherapy is a new fruitful strategy that boosts the ability of the patient's immune system to detect and effectively fight cancer cells. Overcoming immune-suppression by targeting single immune checkpoints (PD-1/L1) has already shown clinical benefit, but patients may develop resistance[31]. Dai and colleagues[32] generated a novel bispecific anti-LAG-3-TIGIT antibody (ZGGS15) and found greater antitumor efficacy in mouse models, compared to targeting LAG-3 and TIGIT alone. Interestingly, ZGGS15 in combination with Nivolumab (anti-PD-1) showed synergistic effects for enhanced T-cell responses and thus inhibited tumor growth in mice. Preclinical safety analyses revealed that ZGGS15 does not induce *cytokine-release syndrome*, which is a serious adverse event of current immunotherapies limiting beneficial therapy responses. Combinatorial immune checkpoint inhibition (ICI) may therefore represent a novel strategy to circumvent immunotherapy resistance. This treatment has sufficiently promising efficacy and warrants further investigation, including in combination with chemotherapy.

The effects of a combination of X-ray or proton irradiation with or without ICI (anti-PD-L1) were investigated in two syngeneic mouse models of head and neck cancer (HNSCC) by Rykkelid et al.[33]. The authors compared therapeutic efficacy on either well-differentiated (immunogenic) or poorly differentiated (less immunogenic) tumors and found synergistic effects of radiation and ICI in both mouse models for both X-ray and proton radiotherapy. The therapeutic benefit of combined X-ray radiotherapy and ICI was pronounced for well-differentiated tumors, whereas the combination of proton radiotherapy and ICI was superior in poorly differentiated tumors. Since radiation is the backbone of current therapeutic options for HNSCC and many patients develop resistance[34], this study illustrated the feasibility of combining radiation with ICI as an effective therapy option.

Tan et al[35] revisited an old target and investigated resistance mechanisms to hypomethylating agents (HMAs) in solid tumors. As clinically approved drugs to treat hematological malignancies, HMAs (e.g. *azacytidine*, *decitabine)* target DNA methyltransferases to reactivate tumor-suppressor genes and double-stranded RNAs[36]. As a result, HMAs show antineoplastic activity through promoting cell differentiation, dampening cell proliferation, and inducing apoptosis via viral mimicry. Unfortunately, HMAs have been shown ineffective in solid tumors, and their molecular mechanisms are not fully understood. Strikingly, this study found increased levels of mitochondrial RNA (mtRNA) and higher metabolic activity promoting ATP production in HMA-treated lung cancer cells. As a consequence, interfering with mitochondrial function through downregulating mature mtRNA expression increased cell death. Searching the needle in the haystack, the authors performed

CRISPR screening and identified *mtRNA-polymerase* and ribonuclease *ELAC2* as new HMA sensitizers by counteracting mtRNA expression and ATP production. Co-treatment with HMA and IMT-1, a small-molecule inhibitor of mtRNA polymerase, led to reduced mtRNA levels and decreased proliferation compared to single HMA and IMT-1 treatment. This study emphasizes the therapeutic advantage of epigenetic reprogramming and co-targeting mitochondrial regulators in solid cancers.

Published online: 24 July 2025

References:

1. DeVita, V. T. Jr. & Chu, E. A history of cancer chemotherapy. *Cancer Res.* **68**, 8643–8653. https://doi.org/10.1158/0008-5472.CAN-07-6611 (2008).
2. Cohen, M. H. et al. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. *Clin. Cancer Res.* **8**, 935–942 (2002).
3. Rosell, R. et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* **13**, 239–246. https://doi.org/10.1016/S1470-2045(11)70393-X (2012).
4. Park, K. et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol.* **17**, 577–589. https://doi.org/10.1016/S1470-2045(16)30033-X (2016).
5. Fan, W., Chang, J. & Fu, P. Endocrine therapy resistance in breast cancer: current status, possible mechanisms and overcoming strategies. *Future Med. Chem.* **7**, 1511–1519. https://doi.org/10.4155/fmc.15.93 (2015).
6. Howell, A. & Howell, S. J. Tamoxifen evolution. *Br. J. Cancer* **128**, 421–425. https://doi.org/10.1038/s41416-023-02158-5 (2023).
7. Hegmans, J. P. & Aerts, J. G. Immunomodulation in cancer. *Curr. Opin. Pharmacol* **17**, 17–21. https://doi.org/10.1016/j.coph.2014.06.007 (2014).
8. Zheng, P. et al. Exosomal transfer of tumor-associated macrophage-derived miR-21 confers cisplatin resistance in gastric cancer cells. *J. Exp. Clin. Cancer Res.* **36**, 53. https://doi.org/10.1186/s13046-017-0528-y (2017).
9. Zhang, T., Zhang, P. & Li, H. X. CAFs-derived exosomal miRNA-130a confers cisplatin resistance of NSCLC cells through PUM2-dependent packaging. *Int. J Nanomed.* **16**, 561–577. https://doi.org/10.2147/IJN.S271976 (2021).
10. Biegala, L. et al. Targeted inhibition of the ATR/CHK1 pathway overcomes resistance to olaparib and dysregulates DNA damage response protein expression in BRCA2(MUT) ovarian cancer cells. *Sci. Rep.* **13**, 22659. https://doi.org/10.1038/s41598-023-50151-y (2023).
11. Goel, N., Foxall, M. E., Scalise, C. B., Wall, J. A. & Arend, R. C. Strategies in overcoming homologous recombination proficiency and PARP inhibitor resistance. *Mol. Cancer Ther.* **20**, 1542–1549. https://doi.org/10.1158/1535-7163.MCT-20-0992 (2021).
12. Quigley, D. et al. Analysis of circulating cell-free DNA identifies multiclonal heterogeneity of BRCA2 reversion mutations associated with resistance to PARP inhibitors. *Cancer Discov.* **7**, 999–1005. https://doi.org/10.1158/2159-8290.CD-17-0146 (2017).
13. Soberanis Pina, P. & Lheureux, S. Overcoming PARP inhibitor resistance in ovarian cancer. *Int. J. Gynecol. Cancer* **33**, 364–376. https://doi.org/10.1136/ijgc-2022-003698 (2023).
14. Rosell, R. et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N. Engl. J. Med.* **361**, 958–967. https://doi.org/10.1056/NEJMoa0904554 (2009).
15. Wu, Y. L. et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol.* **18**, 1454–1466. https://doi.org/10.1016/S1470-2045(17)30608-3 (2017).
16. Soria, J. C. et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N. Engl. J. Med.* **378**, 113–125. https://doi.org/10.1056/NEJMoa1713137 (2018).
17. La Monica, S. et al. Targeting glucosylceramide synthase induces antiproliferative and proapoptotic effects in osimertinib-resistant NSCLC cell models. *Sci. Rep.* **14**, 6491. https://doi.org/10.1038/s41598-024-57028-8 (2024).
18. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2020. *CA Cancer J. Clin.* **70**, 7–30. https://doi.org/10.3322/caac.21590 (2020).
19. Bryant, H. E. et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* **434**, 913–917. https://doi.org/10.1038/nature03443 (2005).
20. Nakai, K., Hung, M. C. & Yamaguchi, H. A perspective on anti-EGFR therapies targeting triple-negative breast cancer. *Am. J. Cancer Res.* **6**, 1609–1623 (2016).
21. Liu, X. et al. Trop2-targeted therapies in solid tumors: advances and future directions. *Theranostics* **14**, 3674–3692. https://doi.org/10.7150/thno.98178 (2024).
22. Carey, L. A. et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin. Cancer Res.* **13**, 2329–2334. https://doi.org/10.1158/1078-0432.CCR-06-1109 (2007).
23. Hudis, C. A. & Gianni, L. Triple-negative breast cancer: an unmet medical need. *Oncologist* **16**(Suppl 1), 1–11. https://doi.org/10.1634/theoncologist.2011-S1-01 (2011).
24. Cheang, M. C. et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. *Clin. Cancer Res.* **14**, 1368–1376. https://doi.org/10.1158/1078-0432.CCR-07-1658 (2008).
25. Martin, J. C. et al. Aryl hydrocarbon receptor suppresses STING-mediated type I IFN expression in triple-negative breast cancer. *Sci. Rep.* **14**, 5731. https://doi.org/10.1038/s41598-024-54732-3 (2024).
26. Gozgit, J. M. et al. PARP7 negatively regulates the type I interferon response in cancer cells and its inhibition triggers antitumor immunity. *Cancer Cell* **39**(1214–1226), e1210. https://doi.org/10.1016/j.ccell.2021.06.018 (2021).
27. Bianchi-Smiraglia, A. et al. Inhibition of the aryl hydrocarbon receptor/polyamine biosynthesis axis suppresses multiple myeloma. *J. Clin. Invest.* **128**, 4682–4696. https://doi.org/10.1172/JCI70712 (2018).
28. Calistri, N. L. et al. TNBC response to paclitaxel phenocopies interferon response which reveals cell cycle-associated resistance mechanisms. *Sci. Rep-Uk* **15**, 4294. https://doi.org/10.1038/s41598-024-82218-9 (2025).
29. Fina, E. et al. Gene signatures of circulating breast cancer cell models are a source of novel molecular determinants of metastasis and improve circulating tumor cell detection in patients. *J. Exp. Clin. Cancer. Res.* **41**, 78. https://doi.org/10.1186/s13046-022-02259-8 (2022).
30. Mesquita, B. et al. Frequent copy number gains at 1q21 and 1q32 are associated with overexpression of the ETS transcription factors ETV3 and ELF3 in breast cancer irrespective of molecular subtypes. *Breast Cancer Res. Treat* **138**, 37–45. https://doi.org/10.1007/s10549-013-2408-2 (2013).
31. Haddad, A. F., Young, J. S., Gill, S. & Aghi, M. K. Resistance to immune checkpoint blockade: Mechanisms, counter-acting approaches, and future directions. *Semin. Cancer Biol.* **86**, 532–541. https://doi.org/10.1016/j.semcancer.2022.02.019 (2022).
32. Dai, T. et al. A novel anti-LAG-3/TIGIT bispecific antibody exhibits potent anti-tumor efficacy in mouse models as monotherapy or in combination with PD-1 antibody. *Sci. Rep.* **14**, 10661. https://doi.org/10.1038/s41598-024-61477-6 (2024).
33. Rykkelid, A. M. et al. Combination of proton- or X-irradiation with anti-PDL1 immunotherapy in two murine oral cancers. *Sci. Rep.* **14**, 11569. https://doi.org/10.1038/s41598-024-62272-z (2024).

34. Hutchinson, M. N. D., Mierzwa, M. & D'Silva, N. J. Radiation resistance in head and neck squamous cell carcinoma: dire need for an appropriate sensitizer. *Oncogene* **39**, 3638–3649. https://doi.org/10.1038/s41388-020-1250-3 (2020).
35. Tan, S., Kim, S. & Kim, Y. Targeting mitochondrial RNAs enhances the efficacy of the DNA-demethylating agents. *Sci. Rep.* **14**, 30767. https://doi.org/10.1038/s41598-024-80834-z (2024).
36. Duchmann, M. & Itzykson, R. Clinical update on hypomethylating agents. *Int. J. Hematol.* **110**, 161–169. https://doi.org/10.1007/s12185-019-02651-9 (2019).

Author contributions

C.D, J-Y.C and C.G wrote the main manuscript text in collaboration. All authors have reviewed and approved the submitted version of the invited Editorial.

Declarations

Competing interests

The authors declare no competing interests.

Correspondence and requests for materials should be addressed to C.G.