



Editorial: Uncovering Drug Resistance During Cancer Therapy

Haitao Wang^{1*}, Rui-Hong Wang¹, Jian-Guo Zhou^{2,3,4,5}, Weilong Hou¹ and Ada Hang-Heng Wong^{6*}

¹Thoracic Surgery Branch, Center for Cancer Research, National Cancer Institute (NIH), Bethesda, MA, United States, ²Department of Oncology, The Second Affiliated Hospital of Zunyi Medical University, Zunyi, China, ³Translational Radiobiology, Department of Radiation Oncology, Universitätsklinikum Erlangen, Erlangen, Germany, ⁴Department of Radiation Oncology, Universitätsklinikum Erlangen, Erlangen, Germany, ⁵Comprehensive Cancer Center Erlangen-Europäische Metropolregion Nürnberg (EMN), Erlangen, Germany, ⁶AW Medical Co Ltd, Macao, Macao SAR, China

Keywords: cancer, oncology, cancer therapy, drug resistance, next generation sequencing, biomarkers

Editorial on the Research Topic

Uncovering Drug Resistance During Cancer Therapy

Drug resistance is one of the most difficult problems to tackle during cancer therapy because of its multifaceted nature (Vasan, Baselga et al., 2019). Innate drug resistance is generally caused by cancer heterogeneity, and is further complicated by the unique microenvironment and immune landscape of each individual patient. On the other hand, acquired resistance is primarily induced by treatment. The interplay among cancer, its microenvironment and the immune system during the course of treatment unveils the continuous evolution of drug resistance on the temporal scale. Furthermore, the diverse mechanisms of anti-cancer drugs, from targeting cancer proliferation to immune evasion, often trigger drug resistance via distinct courses. Hence, continuous disease monitoring and multi-timepoint sampling became indispensable to interrogate cancer progression and resistance development over the course of treatment.

In this issue, we discussed the molecular mechanisms of drug resistance during cancer therapy. Driver mutations have long been considered the mainstream mechanism of drug resistance development. For instance, the development of RAS mutations to constitutively activate the EGFR/RAS pathway is often seen within weeks during anti-EGFR treatment. However, elucidation of point mutations is insufficient to decipher the cancer landscape, let alone the tumor microenvironment. The advent of sequencing technologies enables broader genome coverage and greater depths to uncover genetic mutations other than point mutations, such as indels and copy number changes, while development of novel sequencing methodologies provides additional information on epigenetic modifications, transcriptional regulation, and so on.

For example, Huang et al., described how the membrane transporter *SLC15A4* could serve as a prognostic biomarker for lung adenocarcinoma patients, even though the mutation rate of *SLC15A* family members is relatively low. This underscores how the increased expression of a transmembrane peptide transporter (Song, Hu et al., 2018) that functions in mTOR-dependent autoantibody production (Kobayashi, Shimabukuro-Demoto et al., 2014) could indicate prognosis. While the basal level of *SLC15A4* is prognostic, Wei et al., demonstrated that *MX2* is upregulated with increasing cancer stage and after renal cell carcinoma cells develop resistance against the anti-angiogenic drug Sunitinib. Prognostic biomarkers do not always correlate with tumorigenesis or cancer progression, but might be by-products of these processes. Pretreatment prognosis suggests innate drug resistance, whereas on-treatment prognosis suggests the development of acquired resistance.

Aside from mRNA expression, microRNAs also play important roles in cancer drug resistance (Si, Shen et al., 2019). Tang et al., described how the microRNA processing protein encoded by *hnRNPA2B1* is upregulated in colon cancer to promote cancer progression via the MAPK pathway. Zheng et al., depicted several microRNAs that are positively correlated to *MSM O 1* expression, which is positively correlated to tumor burden and poor prognosis in cervical squamous cell carcinoma. To date, microRNAs contribute

OPEN ACCESS

Edited and reviewed by:

Zhe-Sheng Chen,
St. John's University, United States

*Correspondence:

Haitao Wang
haitao.wang@nih.gov
Ada Hang-Heng Wong
synxin2008@gmail.com

Specialty section:

This article was submitted to
Cancer Genetics and Oncogenomics,
a section of the journal
Frontiers in Genetics

Received: 17 May 2022

Accepted: 23 June 2022

Published: 19 July 2022

Citation:

Wang H, Wang R-H, Zhou J-G, Hou W
and Wong AH-H (2022) Editorial:
Uncovering Drug Resistance During
Cancer Therapy.
Front. Genet. 13:945842.
doi: 10.3389/fgene.2022.945842

to cancer drug resistance mainly through regulation of gene expression. While some microRNAs directly bind to complementary mRNAs to silence gene expression, others cooperate with long non-coding RNAs to fine tune gene expression.

The mechanisms of drug resistance are nonetheless related to the type of anti-cancer drug. While broad-spectrum chemotherapy and targeted therapy inadvertently focus on pathways related to cancer proliferation, sole characterization of cancer cells would leave out important players in the tumor microenvironment that are critical to the development of drug resistance towards immunotherapy. Even though these players may or may not be direct targets of immunotherapy, they contribute to the success of immunotherapy. Wang et al., reviewed various mechanisms of immunotherapy resistance in glioblastoma, such as the infiltration of M2-type tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). TAMs are suggested to promote drug resistance by modulating the cancer stem cell (CSC) population and suppress the immune system via interactions with cytotoxic and regulatory T cells (Petty and Yang 2017). On the other hand, polymorphonuclear MDSCs, which represents 80% of all MDSCs in the majority of cancer types, mainly suppress T cells (Gabrilovich 2017). Hence, cancer evolves to recruit the host immune system to counteract the effects of immunotherapy. Other non-immune players include cancer-associated fibroblasts (CAFs) that secrete growth factors and cytokines to promote tumor growth in breast cancer (Cosentino, Plantamura et al., 2021). Unequivocally, investigation of the tumor microenvironment and the immunological crosstalk is critical to broaden our understanding of the mechanisms of acquired drug resistance.

Therefore, novel sequencing technologies based on single cells and *in situ* hybridization are developed. These technologies provide details to identify and characterize the tumor microenvironment

with unprecedented resolution in terms of cell type and spatial localization. Nevertheless, the enhanced resolution also posits new feasibility problems during clinical translation because it is impossible for any physician to interpret an innumerable list of biomarkers to their patients. Hence, dimensionality reduction by the application of ratiometric parameters comes into play. For example, Wang et al., used the ratio of *SIRT4/SIRT6* mRNA expression to serve as prognostic biomarkers for serous ovarian cancer. While both *SIRT4* and *SIRT6* are histone deacetylases of the sirtuin family, *SIRT4* acts as a tumor suppressor to repress glutamine metabolism (Csibi, Fendt et al., 2013; Jeong, Xiao et al., 2013), a key energy source for cancer cells, whereas *SIRT6* exhibits context-dependent pleiotropic roles in cancer (Fiorentino, Carafa et al., 2021). The combination of these two biomarkers with potentially contrasting roles but are functionally linked succeeds in dimensionality reduction. Alternatively, artificial intelligence and computational visualization aids in interpreting complex results, but the *in clinico* application of these methods remains afar.

In conclusion, our understanding of the mechanisms of cancer drug resistance has been consistently broadening and deepening by the advancement of novel technologies and methodologies that no longer limits to genetics, but also encompasses epigenetic and transcriptional mechanisms. We foresee that future integration of omic technologies will further expands our understanding of cancer drug resistance.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

- Cosentino, G., Plantamura, I., Tagliabue, E., Iorio, M. V., and Cataldo, A. (2021). Breast Cancer Drug Resistance: Overcoming the Challenge by Capitalizing on MicroRNA and Tumor Microenvironment Interplay. *Cancers (Basel)* 13 (15), 3691. doi:10.3390/cancers13153691
- Csibi, A., Fendt, S.-M., Li, C., Poulgiannis, G., Choo, A. Y., Chapski, D. J., et al. (2013). The mTORC1 Pathway Stimulates Glutamine Metabolism and Cell Proliferation by Repressing *SIRT4*. *Cell* 153 (4), 840–854. doi:10.1016/j.cell.2013.04.023
- Fiorentino, F., Carafa, V., Favale, G., Altucci, L., Mai, A., and Rotili, D. (2021). The Two-Faced Role of *SIRT6* in Cancer. *Cancers (Basel)* 13 (5), 1156. doi:10.3390/cancers13051156
- Gabrilovich, D. I. (2017). Myeloid-Derived Suppressor Cells. *Cancer Immunol. Res.* 5 (1), 3–8. doi:10.1158/2326-6066.cir-16-0297
- Jeong, S. M., Xiao, C., Finley, L. W. S., Lahusen, T., Souza, A. L., Pierce, K., et al. (2013). *SIRT4* Has Tumor-Suppressive Activity and Regulates the Cellular Metabolic Response to DNA Damage by Inhibiting Mitochondrial Glutamine Metabolism. *Cancer Cell* 23 (4), 450–463. doi:10.1016/j.ccr.2013.02.024
- Kobayashi, T., Shimabukuro-Demoto, S., Yoshida-Sugitani, R., Furuyama-Tanaka, K., Karyu, H., Sugiyama, Y., et al. (2014). The Histidine Transporter SLC15A4 Coordinates mTOR-dependent Inflammatory Responses and Pathogenic Antibody Production. *Immunity* 41 (3), 375–388. doi:10.1016/j.immuni.2014.08.011
- Petty, A. J., and Yang, Y. (2017). Tumor-associated Macrophages: Implications in Cancer Immunotherapy. *Immunotherapy* 9 (3), 289–302. doi:10.2217/imt-2016-0135
- Si, W., Shen, J., Zheng, H., and Fan, W. (2019). The Role and Mechanisms of Action of microRNAs in Cancer Drug Resistance. *Clin. Epigenet* 11 (1), 25. doi:10.1186/s13148-018-0587-8
- Song, F., Hu, Y., Wang, Y., Smith, D. E., and Jiang, H. (2018). Functional Characterization of Human Peptide/Histidine Transporter 1 in Stably Transfected MDCK Cells. *Mol. Pharm.* 15 (2), 385–393. doi:10.1021/acs.molpharmaceut.7b00728
- Vasan, N., Baselga, J., and Hyman, D. M. (2019). A View on Drug Resistance in Cancer. *Nature* 575 (7782), 299–309. doi:10.1038/s41586-019-1730-1

Conflict of Interest: AW is a founder and shareholder of AW Medical Co Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang, Wang, Zhou, Hou and Wong. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.