

Drug Resistance and Novel Therapies in Cancers in 2019

Zhixiang Wang

Signal Transduction Research Group, Department of Medical Genetics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB T6G 2H7, Canada; zwang@ualberta.ca

After the successful launch in the second half of 2018 by *Cancers*, the topic collection “Drug Resistance and Novel Therapies in Cancers” experienced its productive first full year in 2019.

In 2019, a total of 34 cutting-age research articles and comprehensive review papers had been published under this topic collection. The 26 original research articles covered 13 different cancer types including melanoma [1–4], breast cancer [5–8], colorectal cancer (CRC) [9–11], hepatocellular carcinoma [12–14], glioblastoma [15,16], non-small cell lung cancer (NSCLC) [17,18], prostate cancer [19], ovarian cancer [20], pleural mesothelioma [21], cervical cancer [22], Leukemia [23], adenoid cystic carcinoma [24], and vulvar cancer [25]. While these studies looked at a broad range of cancer therapies including cytotoxic chemotherapy [7,8,11,16,20], electrochemotherapy [25], radio therapy [2,4,18], proton beam therapy [24], and oncolytic virus therapy [6], the most studied are targeted therapies with various means. The cellular process being targeted include glucose metabolism [19], cell signaling [5], endoplasmic reticulum (ER) stress [21], autophagy [12], angiogenesis [10], DNA repair [4,6], apoptosis [11], and microRNA [10,26]. The molecules being targeted include HER2 [5], VEGF [10], p53 [4,13,18], CDK [14], BCR-ABL1 and PAK1/2 [23], PARP1/HMGB1 [12], mir-221 [26], miR-31-5p [10], TIMP-1 [17], Fox3a [8], and FOXC1 [10].

Most of these research articles are well cited, which indicates the significance of their findings. The study regarding the role of FOXC1 regulation of miR-31-5p in oxaliplatin resistance by Huang’s group was cited 13 times within a year of publication [10]. Oxaliplatin (OXA) is currently used in first-line chemotherapy to treat stage III and stage IV metastatic CRC. In this research, the authors studied the role of miRNA in the drug resistance mechanism in an OXA-resistant CRC cell model and in a xenograft animal model. They showed that the upregulated expression of FOXC1 and miR-31-5p inhibited LATS2 expression, which led to OXA resistance. They further showed that the knockdown of miR-31-5p resulted in cancer cell apoptosis, decreased cell proliferation, and enhanced chemosensitivity. These results revealed a novel drug-resistance mechanism in which miR-31-5p and its transcription factor regulate cancer cell growth and apoptosis by targeting LATS2.

In another well-cited piece of research, Singh et al studied therapeutic potential of a natural flavonoid morin hydrate against cisplatin-induced toxicity by using the HepG2DR multi-drug resistant cell line [12]. They showed that dysregulated expression of PARP1 confers cisplatin-resistance via autophagy activation in HepG2DR cells. Morin hydrate inhibits cisplatin-mediated autophagy induction, resulting in increased susceptibility of HepG2DR cells to cisplatin cytotoxicity. This research suggests that the combination of morin hydrate with cisplatin may be a promising therapeutic strategy to enhance the efficacy of conventional chemotherapeutic drugs.

In another well-cited novel study, Xu et al explored novel target for treating malignant pleural mesothelioma (MPM), a rare malignant cancer [21]. They found that ER stress

Citation: Wang, Z. Drug Resistance and Novel Therapies in Cancers. *Cancers* **2021**, *13*, 924. <https://doi.org/10.3390/cancers13040924>

Received: 29 January 2021

Accepted: 23 February 2021

Published: 23 February 2021

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

and the adaptive unfolded protein response (UPR) signaling are characteristically deregulated in MPM. Consequently, pharmacological perturbation of ER stress/UPR axis by HA15, an agent that induces persistent proteotoxic stress in the ER, selectively suppresses the viability of MPM cells. Their findings revealed that HA15 could be used to target ER stress signaling and serve as a promising agent to treat patients with MPM.

In a study aiming to understand the molecular mechanisms underlying the action of pertuzumab and its combination with trastuzumab, Nami et al [5] showed that pertuzumab had no significant effect on HER2 homodimerization; however, trastuzumab increased HER2 homodimerization. Pertuzumab, but not trastuzumab, abrogated the effect of HER2 overexpression on cell cycle progression, whereas trastuzumab abolished the inhibitory effect of HER2 on apoptosis. These results suggested that the clinical effects of pertuzumab may mostly, through the inhibition of HER2 heterodimers, rather than HER2 homodimers and that pertuzumab binding to HER2, may inhibit non-canonical HER2 activation and function in non-HER-mediated and dimerization-independent pathway(s).

Among the three studies regarding p53, one study showed that p53 DNA binding domain mutations predicted progression-free survival of bevacizumab therapy in metastatic CRC [10]. Another study assessed the potential benefit of adding radiotherapy to BRAF-mutated melanoma cells under a combined p53 reactivation and MAPK inhibition and showed that the combination of BRAF inhibition together with p53 reactivation significantly enhanced the radiosensitivity of BRAF-mutant melanoma cells [4]. The third study showed that SLMP53-2 restores the function of mutant p53 through Hsp70 in hepatocellular carcinoma [13].

There were eight comprehensive reviews published in 2019 and most of them are well cited. One review article aimed to discuss the PI3K/AKT/mTOR and CDK4/6 pathways in endocrine resistant HR+/HER2– metastatic breast cancer [27]. In this review, the authors analyzed the PI3K/AKT/mTOR and CDK4/6 pathways and their roles in endocrine resistant metastatic breast cancer. The review focused on the new therapeutic agents developed and the roles of these agents in overcoming endocrine resistance. The central nervous system (CNS) is considered as a sanctuary site, protected from systemic chemotherapy by the meninges, the cerebrospinal fluid (CSF) and the blood–brain barrier (BBB). In one review, the authors described the different strategies developed to improve delivery of antineoplastic agents into the brain in primary and metastatic CNS tumors [28]. DNA damage leads to cancer development and RAD52 has a crucial role in repairing DNA damage. In the review regarding RAD52 functions in homologous recombination and in cancer therapy, Nogueira et al discussed recent reports regarding the role of up- and down-regulation of RAD52 in carcinogenic processes and in targeting RAD52 to improve cancer therapy efficacy [29]. Two reviews focused on CRC. One reviewed the current literature on angioregulatory miRNAs in CRC [30] and the other one is about the tumor microenvironment in CRC therapy [31]. The other three reviews discussed resistance in various cancers. One focused on overcoming drug resistance by pressurized intraperitoneal aerosol chemotherapy (PIPAC) [32], one reviewed therapeutic challenges in managing cisplatin-resistant ovarian germ cell tumors [33], and one examined the resistance to systemic agents in renal cell carcinoma [34].

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Jäger, K.; Larribère, L.; Wu, H.; Weiss, C.; Gebhardt, C.; Utikal, J. Expression of Neural Crest Markers GLDC and ERRFI1 is Correlated with Melanoma Prognosis. *Cancers* 2019, 11, 76.
2. Murata, H.; Okonogi, N.; Wakatsuki, M.; Kato, S.; Kiyohara, H.; Karasawa, K.; Ohno, T.; Nakano, T.; Kamada, T.; Shozu, M., et al. Long-Term Outcomes of Carbon-Ion Radiotherapy for Malignant Gynecological Melanoma. *Cancers* 2019, 11, 482.
3. Karwaciak, I.; Salkowska, A.; Karaś, K.; Sobalska-Kwapis, M.; Walczak-Drzewiecka, A.; Pułaski, Ł.; Strapagiel, D.; Dastyh, J.; Ratajewski, M. SIRT2 Contributes to the Resistance of Melanoma Cells to the Multikinase Inhibitor Dasatinib. *Cancers* 2019, 11, 673.

4. Krayem, M.; Sabbah, M.; Najem, A.; Wouters, A.; Lardon, F.; Simon, S.; Sales, F.; Journe, F.; Awada, A.; Ghanem, G.E., et al. The Benefit of Reactivating p53 under MAPK Inhibition on the Efficacy of Radiotherapy in Melanoma. *Cancers* 2019, 11, 1093.
5. Nami, B.; Maadi, H.; Wang, Z. The Effects of Pertuzumab and Its Combination with Trastuzumab on HER2 Homodimerization and Phosphorylation. *Cancers* 2019, 11, doi:10.3390/cancers11030375.
6. Caccuri, F.; Sommariva, M.; Marsico, S.; Giordano, F.; Zani, A.; Giacomini, A.; Fraefel, C.; Balsari, A.; Caruso, A. Inhibition of DNA Repair Mechanisms and Induction of Apoptosis in Triple Negative Breast Cancer Cells Expressing the Human Herpesvirus 6 U94. *Cancers* 2019, 11, 1006.
7. Suppan, C.; Brcic, I.; Tiran, V.; Mueller, H.D.; Posch, F.; Auer, M.; Ercan, E.; Ulz, P.; Cote, R.J.; Datar, R.H., et al. Untargeted Assessment of Tumor Fractions in Plasma for Monitoring and Prognostication from Metastatic Breast Cancer Patients Undergoing Systemic Treatment. *Cancers* 2019, 11, 1171.
8. Pellegrino, M.; Rizza, P.; Donà, A.; Nigro, A.; Ricci, E.; Fiorillo, M.; Perrotta, I.; Lanzino, M.; Giordano, C.; Bonofiglio, D., et al. FoxO3a as a Positive Prognostic Marker and a Therapeutic Target in Tamoxifen-Resistant Breast Cancer. *Cancers* 2019, 11, 1858.
9. Hsu, H.-C.; You, J.-F.; Chen, S.-J.; Chen, H.-C.; Yeh, C.-Y.; Tsai, W.-S.; Hung, H.-Y.; Yang, T.-S.; Lapke, N.; Tan, K.T. TP53 DNA Binding Domain Mutations Predict Progression-Free Survival of Bevacizumab Therapy in Metastatic Colorectal Cancer. *Cancers* 2019, 11, 1079.
10. Hsu, H.-H.; Kuo, W.-W.; Shih, H.-N.; Cheng, S.-F.; Yang, C.-K.; Chen, M.-C.; Tu, C.-C.; Viswanadha, V.P.; Liao, P.-H.; Huang, C.-Y. FOXC1 Regulation of miR-31-5p Confers Oxaliplatin Resistance by Targeting LATS2 in Colorectal Cancer. *Cancers* 2019, 11, 1576.
11. Lee, Y.-J.; Cho, J.-M.; Sai, S.; Oh, J.Y.; Park, J.-A.; Oh, S.J.; Park, M.; Kwon, J.; Shin, U.S.; Baek, J.-H., et al. 5-Fluorouracil as a Tumor-Treating Field-Sensitizer in Colon Cancer Therapy. *Cancers* 2019, 11, 1999.
12. Singh, M.P.; Cho, H.J.; Kim, J.-T.; Baek, K.E.; Lee, H.G.; Kang, S.C. Morin Hydrate Reverses Cisplatin Resistance by Impairing PARP1/HMGB1-Dependent Autophagy in Hepatocellular Carcinoma. *Cancers* 2019, 11, 986.
13. Gomes, S.; Bosco, B.; Loureiro, J.B.; Ramos, H.; Raimundo, L.; Soares, J.; Nazareth, N.; Barcherini, V.; Domingues, L.; Oliveira, C., et al. SLMP53-2 Restores Wild-Type-Like Function to Mutant p53 through Hsp70: Promising Activity in Hepatocellular Carcinoma. *Cancers* 2019, 11, 1151.
14. Shao, Y.-Y.; Li, Y.-S.; Hsu, H.-W.; Lin, H.; Wang, H.-Y.; Wo, R.R.; Cheng, A.-L.; Hsu, C.-H. Potent Activity of Composite Cyclin Dependent Kinase Inhibition against Hepatocellular Carcinoma. *Cancers* 2019, 11, 1433.
15. Hannen, R.; Selmansberger, M.; Hauswald, M.; Pagenstecher, A.; Nist, A.; Stiewe, T.; Acker, T.; Carl, B.; Nimsky, C.; Bartsch, J.W. Comparative Transcriptomic Analysis of Temozolomide Resistant Primary GBM Stem-Like Cells and Recurrent GBM Identifies Up-Regulation of the Carbonic Anhydrase CA2 Gene as Resistance Factor. *Cancers* 2019, 11, 921.
16. Kim, H.; Chong, K.; Ryu, B.-K.; Park, K.-J.; Yu, M.O.; Lee, J.; Chung, S.; Choi, S.; Park, M.-J.; Chung, Y.-G., et al. Repurposing Penfluridol in Combination with Temozolomide for the Treatment of Glioblastoma. *Cancers* 2019, 11, 1310.
17. Xiao, W.; Wang, L.; Howard, J.; Kolhe, R.; Rojiani, A.M.; Rojiani, M.V. TIMP-1-Mediated Chemoresistance via Induction of IL-6 in NSCLC. *Cancers* 2019, 11, 1184.
18. Van den Bossche, J.; Domen, A.; Peeters, M.; Deben, C.; De Pauw, I.; Jacobs, J.; De Bruycker, S.; Specenier, P.; Pauwels, P.; Vermorken, J.B., et al. Radiosensitization of Non-Small Cell Lung Cancer Cells by the Plk1 Inhibitor Volasertib Is Dependent on the p53 Status. *Cancers* 2019, 11, 1893.
19. Sikander, M.; Malik, S.; Chauhan, N.; Khan, P.; Kumari, S.; Kashyap, V.K.; Khan, S.; Ganju, A.; Halaweish, F.T.; Yallapu, M.M., et al. Cucurbitacin D Reprograms Glucose Metabolic Network in Prostate Cancer. *Cancers* 2019, 11, 364.
20. Chung, W.-M.; Ho, Y.-P.; Chang, W.-C.; Dai, Y.-C.; Chen, L.; Hung, Y.-C.; Ma, W.-L. Increase Paclitaxel Sensitivity to Better Suppress Serous Epithelial Ovarian Cancer via Ablating Androgen Receptor/Aryl Hydrocarbon Receptor-ABCG2 Axis. *Cancers* 2019, 11, 463.
21. Xu, D.; Yang, H.; Yang, Z.; Berezowska, S.; Gao, Y.; Liang, S.-Q.; Marti, T.M.; Hall, S.R.R.; Dorn, P.; Kocher, G.J., et al. Endoplasmic Reticulum Stress Signaling as a Therapeutic Target in Malignant Pleural Mesothelioma. *Cancers* 2019, 11, 1502.
22. Hsin, I.-L.; Chou, Y.-H.; Hung, W.-L.; Ko, J.-L.; Wang, P.-H. The Application of Arsenic Trioxide in Ameliorating ABT-737 Target Therapy on Uterine Cervical Cancer Cells through Unique Pathways in Cell Death. *Cancers* 2020, 12, 108.
23. Flis, S.; Bratek, E.; Chojnacki, T.; Piskorek, M.; Skorski, T. Simultaneous Inhibition of BCR-ABL1 Tyrosine Kinase and PAK1/2 Serine/Threonine Kinase Exerts Synergistic Effect against Chronic Myeloid Leukemia Cells. *Cancers* 2019, 11, 1544.
24. Takayama, K.; Kato, T.; Nakamura, T.; Azami, Y.; Ono, T.; Suzuki, M.; Takada, A.; Yamaguchi, H.; Seto, I.; Nakasato, T., et al. Proton Beam Therapy Combined with Intra-Arterial Infusion Chemotherapy for Stage IV Adenoid Cystic Carcinoma of the Base of the Tongue. *Cancers* 2019, 11, 1413.
25. Perrone, A.M.; Galuppi, A.; Pirovano, C.; Borghese, G.; Covarelli, P.; De Terlizzi, F.; Ferioli, M.; Cara, S.; Morganti, A.G.; De Iaco, P. Palliative Electrochemotherapy in Vulvar Carcinoma: Preliminary Results of the ELECHTRA (Electrochemotherapy Vulvar Cancer) Multicenter Study. *Cancers* 2019, 11, 657.
26. Di Martino, M.T.; Arbitrio, M.; Fonsi, M.; Erratico, C.A.; Scionti, F.; Caracciolo, D.; Tagliaferri, P.; Tassone, P. Allometric Scaling Approaches for Predicting Human Pharmacokinetic of a Locked Nucleic Acid Oligonucleotide Targeting Cancer-Associated miR-221. *Cancers* 2020, 12, 27.
27. Presti, D.; Quaquarelli, E. The PI3K/AKT/mTOR and CDK4/6 Pathways in Endocrine Resistant HR+/HER2- Metastatic Breast Cancer: Biological Mechanisms and New Treatments. *Cancers* 2019, 11, 1242.

28. Triarico, S.; Maurizi, P.; Mastrangelo, S.; Attinà, G.; Capozza, M.A.; Ruggiero, A. Improving the Brain Delivery of Chemotherapeutic Drugs in Childhood Brain Tumors. *Cancers* 2019, 11, 824.
29. Nogueira, A.; Fernandes, M.; Catarino, R.; Medeiros, R. RAD52 Functions in Homologous Recombination and Its Importance on Genomic Integrity Maintenance and Cancer Therapy. *Cancers* 2019, 11, 1622.
30. Soheilifar, M.H.; Grusch, M.; Neghab, H.K.; Amini, R.; Maadi, H.; Saidijam, M.; Wang, Z. Angioregulatory microRNAs in Colorectal Cancer. *Cancers* 2020, 12, 71.
31. Pedrosa, L.; Esposito, F.; Thomson, T.M.; Maurel, J. The Tumor Microenvironment in Colorectal Cancer Therapy. *Cancers* 2019, 11, 1172.
32. Nadiradze, G.; Horvath, P.; Sautkin, Y.; Archid, R.; Weinreich, F.-J.; Königsrainer, A.; Reymond, M.A. Overcoming Drug Resistance by Taking Advantage of Physical Principles: Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). *Cancers* 2020, 12, 34.
33. De Giorgi, U.; Casadei, C.; Bergamini, A.; Attademo, L.; Cormio, G.; Lorusso, D.; Pignata, S.; Mangili, G. Therapeutic Challenges for Cisplatin-Resistant Ovarian Germ Cell Tumors. *Cancers* 2019, 11, 1584.
34. Mollica, V.; Di Nunno, V.; Gatto, L.; Santoni, M.; Scarpelli, M.; Cimadamore, A.; Lopez-Beltran, A.; Cheng, L.; Battelli, N.; Montironi, R., et al. Resistance to Systemic Agents in Renal Cell Carcinoma Predict and Overcome Genomic Strategies Adopted by Tumor. *Cancers* 2019, 11, 830.