

Plasma in Cancer Treatment

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Cancer is the second leading cause of death worldwide, and while science has advanced significantly to improve the treatment outcome and quality of life in cancer patients, there are still many issues with the current therapies, such as toxicity and the development of resistance to treatment. The scientific community conducting oncological research is putting significant efforts into finding new and efficient alternatives in order to reduce the harmful side effects caused by conventional cancer therapies. One of these is cold atmospheric plasma (CAP), which involves the application of an ionized gas, rich in ions, electrons, radicals and excited species, able to eliminate cancerous cells and contribute to healing cancerous lesions [1,2]. Compared to traditional systemic anticancer therapies, CAP can be administered locally and can modulate and activate multiple signaling pathways in cancer cells, which contribute to their elimination [3]. Exciting advances made in the past few years in the field of biomedical plasma have allowed scientists to explore its use in different types of cancer. To date, some of the key events involved in the response to CAP-derived reactive oxygen species (ROS), such as cell death, senescence and cell cycle arrest, among others [4–6], have been identified in cancer cells. However, the response evoked by CAP in different populations of cells (cancerous, stromal, immune cells) varies greatly and selectivity studies could help to unravel this issue. In addition, it is important to consider the three-dimensional nature of solid tumors, where the tumor microenvironment plays an important role in the response to therapy [7].

The scope of CAP for cancer therapy is rapidly expanding to address difficult targets which were previously untreatable, including those with metastatic potential and resistance to drugs. To progress towards a widespread clinical application of CAP, an integrated study of the multi-dimensional effect of CAP in cancer treatment is essential.

This Special Issue on “Plasma in Cancer Treatment” brings together 16 original research papers [8–23] and two insightful reviews [24,25]. The papers published in the Special Issue provide valuable information regarding the efficacy of CAP against osteosarcoma, glioblastoma, cholangiocarcinoma, melanoma, pancreatic, ovarian, breast, cervical and colorectal cancer. The article collection includes studies on the fundamental mechanisms of action during oxidative stress and chemotherapy [12], molecular mechanisms of action [24], cell cycle regulation [25], activation of cell signaling pathways [14], effect on stromal and immune cells [8,17], metastatic potential [23], the tumor microenvironment [17,25] and selectivity of CAP towards cancer cells [22]. CAP has been used in combination with chemotherapeutics and radiation therapy to boost their cytotoxic activity [9,10] and to restore sensitivity to chemotherapeutics [11]. In combination with low pulse electric fields, CAP improves the permeabilization of cells [19], which could be beneficial for drug delivery. The addition of gold quantum dots to CAP treatment can further boost the efficacy of the treatment [13]. In addition, the use of non-thermally operated electrosurgical argon plasma devices for cancer therapy has been explored [15,16], which presents an opportunity to use existing devices for cancer treatment. Three reports have used plasma-treated Ringer’s saline and phosphate buffered-saline (PBS) solutions with anticancer properties, supporting the potential of this alternative treatment modality [18,20,21].

Two review papers complete this Special Issue. The first summarizes the current state of knowledge on the molecular mechanisms of action of CAP [24] and the second explores the role of the tumor microenvironment in the response to CAP treatment and presents useful three-dimensional in vitro culture models for plasma research [25].

In summary, this Special Issue presents the effect of CAP on a wide range of cancer types, highlighting the versatility of CAP and its future application in the field. The studies presented here offer an opportunity to consider the application of CAP in the clinic to improve survival rates and quality of life of cancer patients in the near future.

Conflicts of Interest: The authors declare that the present article also summarizes articles co-authored by them.

References

1. Babaeva, N.Y.; Naidis, G.V. Modeling of Plasmas for Biomedicine. *Trends Biotechnol.* **2018**, *36*, 603–614. [[CrossRef](#)] [[PubMed](#)]
2. Woedtke, T.V.; Schmidt, A.; Bekeschus, S.; Wende, K.; Weltmann, K.-D. Plasma Medicine: A Field of Applied Redox Biology. *In Vivo* **2019**, *33*, 1011–1026. [[CrossRef](#)] [[PubMed](#)]
3. Privat-Maldonado, A.; Schmidt, A.; Lin, A.; Weltmann, K.-D.; Wende, K.; Bogaerts, A.; Bekeschus, S. ROS from Physical Plasmas: Redox Chemistry for Biomedical Therapy. *Oxidative Med. Cell. Longev.* **2019**, *2019*, 29. [[CrossRef](#)]
4. Siu, A.; Volotskova, O.; Cheng, X.; Khalsa, S.S.; Bian, K.; Murad, F.; Keidar, M.; Sherman, J.H. Differential Effects of Cold Atmospheric Plasma in the Treatment of Malignant Glioma. *PLoS ONE* **2015**, *10*, e0126313. [[CrossRef](#)] [[PubMed](#)]
5. Yang, X.; Chen, G.; Yu, K.N.; Yang, M.; Peng, S.; Ma, J.; Qin, F.; Cao, W.; Cui, S.; Nie, L.; et al. Cold atmospheric plasma induces GSDME-dependent pyroptotic signaling pathway via ROS generation in tumor cells. *Cell Death Dis.* **2020**, *11*, 295. [[CrossRef](#)] [[PubMed](#)]
6. Brany, D.; Dvorská, D.; Halašová, E.; Škovierová, H. Cold Atmospheric Plasma: A Powerful Tool for Modern Medicine. *Int. J. Mol. Sci.* **2020**, *21*, 2932. [[CrossRef](#)]
7. Roma-Rodrigues, C.; Mendes, R.; Baptista, P.V.; Fernandes, A.R. Targeting Tumor Microenvironment for Cancer Therapy. *Int. J. Mol. Sci.* **2019**, *20*, 840. [[CrossRef](#)]
8. Van Loenhout, J.; Flieswasser, T.; Boullousa, L.F.; De Waele, J.; Van Audenaerde, J.R.; Marcq, E.; Jacobs, J.; Lin, A.; Lion, E.; Dewitte, H.; et al. Cold Atmospheric Plasma-Treated PBS Eliminates Immunosuppressive Pancreatic Stellate Cells and Induces Immunogenic Cell Death of Pancreatic Cancer Cells. *Cancers* **2019**, *11*, 1597. [[CrossRef](#)]
9. Liedtke, K.R.; Freund, E.; Hermes, M.; Oswald, S.; Heidecke, C.-D.; Partecke, L.-I.; Bekeschus, S. Gas Plasma-Conditioned Ringer's Lactate Enhances the Cytotoxic Activity of Cisplatin and Gemcitabine in Pancreatic Cancer In Vitro and In Ovo. *Cancers* **2020**, *12*, 123. [[CrossRef](#)]
10. Lafontaine, J.; Boisvert, J.-S.; Glory, A.; Coulombe, S.; Wong, P. Synergy between Non-Thermal Plasma with Radiation Therapy and Olaparib in a Panel of Breast Cancer Cell Lines. *Cancers* **2020**, *12*, 348. [[CrossRef](#)]
11. Park, S.; Kim, H.; Ji, H.W.; Kim, H.W.; Yun, S.H.; Choi, E.H.; Kim, S.J. Cold Atmospheric Plasma Restores Paclitaxel Sensitivity to Paclitaxel-Resistant Breast Cancer Cells by Reversing Expression of Resistance-Related Genes. *Cancers* **2019**, *11*, 2011. [[CrossRef](#)] [[PubMed](#)]
12. Freund, E.; Liedtke, K.R.; Miebach, L.; Wende, K.; Heidecke, A.; Kaushik, N.K.; Choi, E.H.; Partecke, L.-I.; Bekeschus, S. Identification of Two Kinase Inhibitors with Synergistic Toxicity with Low-Dose Hydrogen Peroxide in Colorectal Cancer Cells In vitro. *Cancers* **2020**, *12*, 122. [[CrossRef](#)] [[PubMed](#)]
13. Kaushik, N.K.; Choi, E.H.; Wahab, R.; Bhartiya, P.; Nguyen, L.N.; Khan, F.; Al-Khedhairi, A.A.; Choi, E.H. Cold Atmospheric Plasma and Gold Quantum Dots Exert Dual Cytotoxicity Mediated by the Cell Receptor-Activated Apoptotic Pathway in Glioblastoma Cells. *Cancers* **2020**, *12*, 457. [[CrossRef](#)]
14. Akter, M.; Jangra, A.; Choi, S.A.; Choi, E.H.; Han, I. Non-Thermal Atmospheric Pressure Bio-Compatible Plasma Stimulates Apoptosis via p38/MAPK Mechanism in U87 Malignant Glioblastoma. *Cancers* **2020**, *12*, 245. [[CrossRef](#)] [[PubMed](#)]

15. Wenzel, T.; Berrio, D.C.; Reisenauer, C.; Layland, S.; Koch, A.; Wallwiener, D.; Brucker, S.Y.; Schenke-Layland, K.; Brauchle, E.-M.; Weiss, M. Trans-Mucosal Efficacy of Non-Thermal Plasma Treatment on Cervical Cancer Tissue and Human Cervix Uteri by a Next Generation Electrosurgical Argon Plasma Device. *Cancers* **2020**, *12*, 267. [[CrossRef](#)] [[PubMed](#)]
16. Feil, L.; Koch, A.; Utz, R.; Ackermann, M.; Barz, J.; Stope, M.B.; Krämer, B.; Wallwiener, D.; Brucker, S.Y.; Weiss, M. Cancer-Selective Treatment of Cancerous and Non-Cancerous Human Cervical Cell Models by a Non-Thermally Operated Electrosurgical Argon Plasma Device. *Cancers* **2020**, *12*, 1037. [[CrossRef](#)] [[PubMed](#)]
17. Vaquero, J.; Judée, F.; Vallette, M.; Decauchy, H.; Arbelaiz, A.; Aoudjehane, L.; Scatton, O.; Gonzalez-Sanchez, E.; Merabtene, F.; Augustin, J.; et al. Cold-Atmospheric Plasma Induces Tumor Cell Death in Preclinical In Vivo and In Vitro Models of Human Cholangiocarcinoma. *Cancers* **2020**, *12*, 1280. [[CrossRef](#)]
18. Griseti, E.; Merbahi, N.; Teissié, J. Anti-Cancer Potential of Two Plasma-Activated Liquids: Implication of Long-Lived Reactive Oxygen and Nitrogen Species. *Cancers* **2020**, *12*, 721. [[CrossRef](#)]
19. Chung, T.-H.; Stancampiano, A.; Sklias, K.; Gazeli, K.; Andre, F.M.; Dozias, S.; Douat, C.; Pouvesle, J.-M.; Sousa, J.S.; Robert, E.; et al. Cell Electroporation Enhancement by Non-Thermal-Plasma-Treated PBS. *Cancers* **2020**, *12*, 219. [[CrossRef](#)]
20. Mateu-Sanz, M.; Tornin, J.; Brulin, B.; Khlyustova, A.; Ginebra, M.-P.; Layrolle, P.; Canal, C. Cold Plasma-Treated Ringer's Saline: A Weapon to Target Osteosarcoma. *Cancers* **2020**, *12*, 227. [[CrossRef](#)]
21. Bisag, A.; Bucci, C.; Coluccelli, S.; Girolimetti, G.; Laurita, R.; De Iaco, P.; Perrone, A.M.; Gherardi, M.; Marchio, L.; Porcelli, A.M.; et al. Plasma-activated Ringer's Lactate Solution Displays a Selective Cytotoxic Effect on Ovarian Cancer Cells. *Cancers* **2020**, *12*, 476. [[CrossRef](#)] [[PubMed](#)]
22. Biscop, E.; Lin, A.; Van Boxem, W.; Van Loenhout, J.; De Backer, J.; Deben, C.; Dewilde, S.; Smits, E.L.; Bogaerts, A. Influence of Cell Type and Culture Medium on Determining Cancer Selectivity of Cold Atmospheric Plasma Treatment. *Cancers* **2019**, *11*, 1287. [[CrossRef](#)] [[PubMed](#)]
23. Bekeschus, S.; Freund, E.; Spadola, C.; Privat-Maldonado, A.; Hackbarth, C.; Bogaerts, A.; Schmidt, A.; Wende, K.; Weltmann, K.-D.; Von Woedtke, T.; et al. Risk Assessment of kINPen Plasma Treatment of Four Human Pancreatic Cancer Cell Lines with Respect to Metastasis. *Cancers* **2019**, *11*, 1237. [[CrossRef](#)]
24. Semmler, M.L.; Bekeschus, S.; Schäfer, M.; Bernhardt, T.; Fischer, T.; Witzke, K.; Seebauer, C.; Rebl, H.; Grambow, E.; Vollmar, B.; et al. Molecular Mechanisms of the Efficacy of Cold Atmospheric Pressure Plasma (CAP) in Cancer Treatment. *Cancers* **2020**, *12*, 269. [[CrossRef](#)] [[PubMed](#)]
25. Privat-Maldonado, A.; Bengtson, C.; Razzokov, J.; Smits, E.L.; Bogaerts, A. Modifying the Tumour Microenvironment: Challenges and Future Perspectives for Anticancer Plasma Treatments. *Cancers* **2019**, *11*, 1920. [[CrossRef](#)]

