International Journal of
Molecular Sciences

MDPI

Editorial

Enzymes Dysregulation in Cancer: From Diagnosis to Therapeutical Approaches

Valentina Pozzi [1,*], Roberto Campagna [1,*], Davide Sartini [1] and Monica Emanuelli [1,2]

[1] Department of Clinical Sciences, Polytechnic University of Marche, 60131 Ancona, Italy; d.sartini@univpm.it (D.S.); m.emanuelli@univpm.it (M.E.)
[2] New York-Marche Structural Biology Center (NY-MaSBiC), Polytechnic University of Marche, 60131 Ancona, Italy
* Correspondence: v.pozzi@univpm.it (V.P.); r.campagna@univpm.it (R.C.)

The metabolic reprogramming that occurs in cancer cells is a hallmark of cancer [1]. Indeed, elucidating the effects of dysregulated metabolism on cancer cell phenotype constitutes the focus of many researchers. Proliferating malignant cells are highly demanding in terms of energy supply and molecules required to fuel biosynthesis. Thus, cancer cells display significant metabolic alterations to meet the requirements for rapid growth and survival. For instance, cancer cells are characterized by enhanced glycolysis, the so-called "Warburg effect", and glutamine catabolism. The reprogramming of cell metabolism toward a malignant phenotype is the result of a series of downstream events triggered by the mutations of oncogenes or tumor suppressors, dysregulated signal transduction pathways, and altered nutrient availability in the tumor microenvironment [2,3].

Despite the continuous accumulation of mutations responsible for intra- and inter-tumor heterogeneity, the dysregulation of specific enzymes can be a distinguished feature for some groups of malignancies [4–6]. Among the enzymes that play a key role in the proliferation and aggressiveness of malignant cells there are glycolytic enzymes like lactate dehydrogenase (LDH), caspases, cyclin-dependent kinases, redox–detox enzymes and NAD^+-dependent enzymes [7,8]. In recent years, several enzymes emerged as potential biomarkers for the diagnosis or prognosis of several malignancies [9–14]. Moreover, the possibility of designing specific inhibitors has also opened the possibility of utilizing these biomarkers as therapeutic targets [15–18]. The need to discover novel enzymatic pathways dysregulated in cancer, as well as identifying novel potential therapeutic targets for cancer management, was highlighted by several papers published in this Special Issue.

The works published by Tossetta et al. reviewed the pathophysiology, treatment options and novel biomarkers in ovarian cancer. In particular, authors focused on the dysregulated enzymatic pathways responsible for the enhanced chemoresistance of ovarian cancer cells. The authors focused on the role of metformin, which exerts important anti-cancer effects in malignant cells as an inhibitor of respiratory chain complex I, which in turn oxidizes the NADH yielded through the Krebs cycle. Moreover, it has been demonstrated that this molecule significantly restores drug sensitivity in ovarian cancer cells that display resistance to paclitaxel and platinum-derived drugs [19].

The same research group reviewed the effect of the antioxidant enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1), whose expression is mainly regulated by nuclear factor erythroid 2-related factor 2 (NRF2), a transcription factor that plays a key role in ovarian cancer onset and progression [20,21]. Authors underlined how the NQO1 enzyme could be a promising therapeutic target in ovarian cancer since it plays a pivotal role in ovarian cancer progression and chemotherapeutic response, utilizing glutaminase inhibitors such as CB-839 to suppress NRF2/NQO1-mediated pathways and enhance the chemosensitivity of ovarian cancer cells [22].

Chen et al. reviewed the current literature about the impact of glutathione peroxidase 4 (GPX4) on cancer cell ferroptosis, a form of iron-dependent cell death consequent to high

check for updates

Citation: Pozzi, V.; Campagna, R.; Sartini, D.; Emanuelli, M. Enzymes Dysregulation in Cancer: From Diagnosis to Therapeutical Approaches. *Int. J. Mol. Sci.* **2023**, *24*, 13815. https://doi.org/10.3390/ijms241813815

Received: 5 September 2023
Accepted: 6 September 2023
Published: 7 September 2023

Copyright: © 2023 by the authors. 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 (https://creativecommons.org/licenses/by/4.0/).

iron accumulation and lipid peroxidation. The authors reported how GPX4 displays an excellent antioxidant capacity in preventing ferroptosis. This is in line with the evidence that GPX4 expression levels are higher in several types of cancer cells compared to normal tissues, allowing cells to counteract ferroptosis more efficiently. For these reasons, the inhibition of the GPX4 pathway could represent an effective strategy for anti-cancer therapy. Thus, there is ongoing research that aims to characterize efficient GPX4 inhibitors for clinical tests [23].

In an interesting experimental work, Dalpatraj et al. investigated the use of GSK-J4, a H3K27 demethylase (JMJD3/KDM6B) inhibitor to study its effects on TGFβ-induced epithelial-to-mesenchymal transition (EMT) in prostate cancer cells. Tests were either performed alone or in combination with phytochemical hesperetin, a citrus bioflavonoid. The researchers found that coupling hesperetin and GSK-J4 treatment at lower doses effectively prevented TGFβ-induced migration and the invasion of the prostate cancer cells, effects that were associated with epigenetic modifications [24].

Manna et al. demonstrated with an elegant study that the steroidogenic acute regulatory (StAR) protein is differentially expressed in tumor and non-tumor human and mouse breast cells/tissues, highlighting the potential role of this cholesterol transporter as a novel diagnostic biomarker for breast cancer. Moreover, they demonstrated that a number of histone deacetylase inhibitors (HDACIs) were efficient in suppressing StAR and also estrogen levels in vitro. This was found not only in hormone-sensitive human breast cancer cells, but also in primary cultures of breast cancer epithelial cells, suggesting StAR's possible therapeutic utility as a drug target for the treatment of breast cancer [25].

Finally, Lucia et al. elaborated a complex but novel thermodynamic approach to the epigenomics of cancer metabolism based on the consumption of metabolites to reverse the membrane electric potential required to sustain cell activity, a process driven by ion fluxes. Furthermore, they analytically demonstrated the correlation between cell proliferation and membrane electric potential through a thermodynamic approach, emphasizing how its modulation is associated with the inflow and outflow of ions [26].

Altogether, this Special Issue collected interesting experimental and review articles that will be of interest to the scientific community.

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

References

1. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. *Cell* **2011**, *144*, 646–674. [CrossRef] [PubMed]
2. Perez-Gonzalez, A.; Bevant, K.; Blanpain, C. Cancer cell plasticity during tumor progression, metastasis and response to therapy. *Nat. Cancer* **2023**, *4*, 1063–1082. [CrossRef]
3. Hoxhaj, G.; Manning, B.D. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. *Nat. Rev. Cancer* **2020**, *20*, 74–88. [CrossRef] [PubMed]
4. Oliveira, R.I.; Guedes, R.A.; Salvador, J.A.R. Highlights in USP7 inhibitors for cancer treatment. *Front. Chem.* **2022**, *10*, 1005727. [CrossRef] [PubMed]
5. Campagna, R.; Pozzi, V.; Salvucci, A.; Togni, L.; Mascitti, M.; Sartini, D.; Salvolini, E.; Santarelli, A.; Lo Muzio, L.; Emanuelli, M. Paraoxonase-2 expression in oral squamous cell carcinoma. *Hum. Cell* **2023**, *36*, 1211–1213. [CrossRef] [PubMed]
6. Li, G.; Li, D.; Wang, T.; He, S. Pyrimidine Biosynthetic Enzyme CAD: Its Function, Regulation, and Diagnostic Potential. *Int. J. Mol. Sci.* **2021**, *22*, 10253. [CrossRef]
7. Baig, M.H.; Adil, M.; Khan, R.; Dhadi, S.; Ahmad, K.; Rabbani, G.; Bashir, T.; Imran, M.A.; Husain, F.M.; Lee, E.J.; et al. Enzyme targeting strategies for prevention and treatment of cancer: Implications for cancer therapy. *Semin. Cancer Biol.* **2019**, *56*, 1–11. [CrossRef] [PubMed]
8. Campagna, R.; Vignini, A. NAD(+) Homeostasis and NAD(+)-Consuming Enzymes: Implications for Vascular Health. *Antioxidants* **2023**, *12*, 376. [CrossRef] [PubMed]
9. Sartini, D.; Campagna, R.; Lucarini, G.; Pompei, V.; Salvolini, E.; Mattioli-Belmonte, M.; Molinelli, E.; Brisigotti, V.; Campanati, A.; Bacchetti, T.; et al. Differential immunohistochemical expression of paraoxonase-2 in actinic keratosis and squamous cell carcinoma. *Hum. Cell* **2021**, *34*, 1929–1931. [CrossRef] [PubMed]
10. Zhou, Q.; Ye, F.; Zhou, Y. Oxidative stress-related biomarkers in oral squamous cell carcinoma patients: A systematic review and meta-analysis. *Biomark. Med.* **2023**, *17*, 337–347. [CrossRef] [PubMed]

11. Campagna, R.; Belloni, A.; Pozzi, V.; Salvucci, A.; Notarstefano, V.; Togni, L.; Mascitti, M.; Sartini, D.; Giorgini, E.; Salvolini, E.; et al. Role Played by Paraoxonase-2 Enzyme in Cell Viability, Proliferation and Sensitivity to Chemotherapy of Oral Squamous Cell Carcinoma Cell Lines. *Int. J. Mol. Sci.* **2022**, *24*, 338. [CrossRef] [PubMed]
12. Garcia-Hernandez, L.; Garcia-Ortega, M.B.; Ruiz-Alcala, G.; Carrillo, E.; Marchal, J.A.; Garcia, M.A. The p38 MAPK Components and Modulators as Biomarkers and Molecular Targets in Cancer. *Int. J. Mol. Sci.* **2021**, *23*, 370. [CrossRef] [PubMed]
13. Kubik, A.; das Virgens, I.P.A.; Szabo, A.; Varadi, M.; Csizmarik, A.; Keszthelyi, A.; Majoros, A.; Fehervari, P.; Hegyi, P.; Acs, N.; et al. Comprehensive Analysis of the Prognostic Value of Circulating MMP-7 Levels in Urothelial Carcinoma: A Combined Cohort Analysis, Systematic Review, and Meta-Analysis. *Int. J. Mol. Sci.* **2023**, *24*, 7859. [CrossRef] [PubMed]
14. Campagna, R.; Pozzi, V.; Giorgini, S.; Morichetti, D.; Goteri, G.; Sartini, D.; Serritelli, E.N.; Emanuelli, M. Paraoxonase-2 is upregulated in triple negative breast cancer and contributes to tumor progression and chemoresistance. *Hum. Cell* **2023**, *36*, 1108–1119. [CrossRef] [PubMed]
15. Lee, J.S.; Hackbart, H.; Cui, X.; Yuan, Y. CDK4/6 Inhibitor Resistance in Hormone Receptor-Positive Metastatic Breast Cancer: Translational Research, Clinical Trials, and Future Directions. *Int. J. Mol. Sci.* **2023**, *24*, 11791. [CrossRef] [PubMed]
16. van Haren, M.J.; Gao, Y.; Buijs, N.; Campagna, R.; Sartini, D.; Emanuelli, M.; Mateuszuk, L.; Kij, A.; Chlopicki, S.; Escude Martinez de Castilla, P.; et al. Esterase-Sensitive Prodrugs of a Potent Bisubstrate Inhibitor of Nicotinamide N-Methyltransferase (NNMT) Display Cellular Activity. *Biomolecules* **2021**, *11*, 1357. [CrossRef] [PubMed]
17. Musicco, C.; Signorile, A.; Pesce, V.; Loguercio Polosa, P.; Cormio, A. Mitochondria Deregulations in Cancer Offer Several Potential Targets of Therapeutic Interventions. *Int. J. Mol. Sci.* **2023**, *24*, 10420. [CrossRef]
18. van Haren, M.J.; Zhang, Y.; Thijssen, V.; Buijs, N.; Gao, Y.; Mateuszuk, L.; Fedak, F.A.; Kij, A.; Campagna, R.; Sartini, D.; et al. Macrocyclic peptides as allosteric inhibitors of nicotinamide N-methyltransferase (NNMT). *RSC Chem. Biol.* **2021**, *2*, 1546–1555. [CrossRef] [PubMed]
19. Tossetta, G. Metformin Improves Ovarian Cancer Sensitivity to Paclitaxel and Platinum-Based Drugs: A Review of In Vitro Findings. *Int. J. Mol. Sci.* **2022**, *23*, 12893. [CrossRef]
20. Tossetta, G.; Fantone, S.; Montanari, E.; Marzioni, D.; Goteri, G. Role of NRF2 in Ovarian Cancer. *Antioxidants* **2022**, *11*, 663. [CrossRef] [PubMed]
21. Tossetta, G.; Marzioni, D. Natural and synthetic compounds in Ovarian Cancer: A focus on NRF2/KEAP1 pathway. *Pharmacol. Res.* **2022**, *183*, 106365. [CrossRef]
22. Tossetta, G.; Fantone, S.; Goteri, G.; Giannubilo, S.R.; Ciavattini, A.; Marzioni, D. The Role of NQO1 in Ovarian Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 7839. [CrossRef]
23. Chen, M.; Shi, Z.; Sun, Y.; Ning, H.; Gu, X.; Zhang, L. Prospects for Anti-Tumor Mechanism and Potential Clinical Application Based on Glutathione Peroxidase 4 Mediated Ferroptosis. *Int. J. Mol. Sci.* **2023**, *24*, 1607. [CrossRef]
24. Dalpatraj, N.; Naik, A.; Thakur, N. Combination Treatment of a Phytochemical and a Histone Demethylase Inhibitor-A Novel Approach towards Targeting TGFbeta-Induced EMT, Invasion, and Migration in Prostate Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 1860. [CrossRef]
25. Manna, P.R.; Ramachandran, S.; Pradeepkiran, J.A.; Molehin, D.; Castro-Piedras, I.; Pruitt, K.; Ganapathy, V.; Reddy, P.H. Expression and Function of StAR in Cancerous and Non-Cancerous Human and Mouse Breast Tissues: New Insights into Diagnosis and Treatment of Hormone-Sensitive Breast Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 758. [CrossRef]
26. Lucia, U.; Deisboeck, T.S.; Ponzetto, A.; Grisolia, G. A Thermodynamic Approach to the Metaboloepigenetics of Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 3337. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.