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Commentary

Electron Transfer-Based Compounds: A Novel Weapon in the Cancer Battlespace?☆

A. Neesse*, E. Hessmann

Dept. Gastroenterology and Gastrointestinal Oncology, University Medical Centre Goettingen, Georg August University Goettingen, Germany

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In 1971, US President Nixon announced the "war on cancer". This declaration not only sparked global interest in this devastating disease but also fuelled large investments. Interdisciplinary and international consortia in academic and commercial cancer research and drug development were fostered around the world. Some 40 years later, our understanding of the cellular and molecular pathophysiology of many cancer entities has tremendously increased (Hanahan and Weinberg, 2011). This impressive knowledge has led to the establishment of cancer prevention programs, early diagnostics and more effective treatment strategies. However, despite astonishing improvements in certain entities such as cervical, -prostate, and breast cancer, the war on cancer has not been won (Hanahan, 2014). In the US, a total of 1,658,370 new cancer cases and 589,430 cancer deaths are anticipated to occur in 2015 (Siegel et al., 2015). Due to the growth and aging of the world population, cancer becomes a global economic problem. In Europe more than US$ 67 billion are spent for cancer patients each year (Luengo-Fernandez et al., 2013).

Several treatment modalities have been developed and refined for cancer patients depending on the cancer type, stage, molecular and histological subtype and other co-morbidities of the patient. Apart from surgery, medical oncological treatment normally encompasses chemotherapy, radiotherapy, targeted therapies, or a combination of the aforementioned. Targeted therapies aim to disrupt certain signaling pathways and epigenetic mechanisms that are dysregulated in cancer cells and drive hallmark features such as tumor growth, progression and spread. Apart from remarkable exceptions (e.g. chronic myeloid leukemia), many targeted therapies fail to achieve long-lasting remissions and cancer cells become resistant to treatment over time. Chemo- and radiotherapy target cancer cells less selectively by interfering with the replicative cellular machinery of highly proliferative cancer cells. Besides innate and required resistance, one obvious disadvantage of this unselective cell killing is the fact that healthy proliferating cells such as intestinal, hematopoietic- or hair follicle cells are also eliminated by chemo-and radiotherapy thus accounting for most of the acute side effects. Unfortunately, the induction of DNA damage in living cells may also lead to carcinogenic effects itself that only become overt several years after the termination of chemo- and radiotherapy by the occurrence of secondary tumors.

Cisplatin [$Pt(NH_3)_2Cl_2$] is a widely used platinum-based chemotherapeutic agent that is used to treat a variety of cancers such as lung, cervical, ovarian or head and neck cancers. The cytotoxicity of cisplatin has been attributed to its ability to bind the *cis*-[$Pt(NH_3)_2$] unit to DNA. However, cisplatin is also known as a radiosensitizing agent that augments the DNA damaging effects of radiotherapy. Upon high energy radiation of living cells, hydroxyl radicals (OH•) and free electrons with high kinetic energy are generated. As electrons become hydrated (e^-_{hyd}) quickly, OH• radicals have long been understood to be causative for DNA damage upon irradiation. However, femtosecond ($1\ fs = 10^{-15}$) time-resolved laser spectroscopy (fs-TRLS) has revealed a short lived prehydrated state (e^-_{pre}) of free electrons that lasts less than a picosecond ($=10^{-12}$ s) before hydration occurs (Migus et al., 1987). Despite the fact that e^-_{pre} has lost their kinetic energy, they form anions with nucleotides, predominantly $dGMP^-$ and $dTMP^-$, that dissociate thus inducing single- and double-strand breaks in DNA (Wang et al., 2009). This reductive DNA damage mechanism was termed dissociative-electron-transfer (DET) and was also shown for cisplatin where ultrashort-lived e^-_{pre} form *cis*-$Pt(NH_3)_2Cl$• or *cis*-$Pt(NH_3)_2$• radicals leading to the formation of transient anions at cisplatin's binding site of DNA and subsequent DNA damage (Lu et al., 2007). The discovery of this mechanism may have important implications for the design of novel anti-cancer therapies as weakly bound electrons may be intrinsically abundant in cancer cells thus sparing normal cells from DET induced DNA damage.

Indeed, in this issue of *EBioMedicine*, Lu et al. report the discovery of a new class of non-platinum-based compounds that comprise an aromatic ring coupled to two NH_2 groups as the electron transfer promoter and one or more halogen atoms (Lu et al., 2015). The absence of the heavy metal platinum as coordinating ion results in a significantly reduced toxicity, while the novel so called femtomedicine (FMD) compounds

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* Corresponding author at: Department of Gastroenterology and Gastrointestinal Oncology, University Medical Center Goettingen, Robert Koch Str. 40, 37075 Goettingen, Germany.

E-mail address: albrecht.neesse@med.uni-goettingen.de (A. Neesse).

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may be highly effective in DET reaction with weakly-bound electrons. Using cervical, breast, ovarian and lung cancer cell lines and xenograft tumors, the authors elegantly show significant cytotoxicity of novel FMD compounds against cancer cells in vitro and pronounced delay of tumor growth in vivo. Mechanistically, FMD compounds led to DNA damage, cell cycle arrest in the S-phase and programmed cell death. Compared to cisplatin, non-platinum-based FMD compounds were less efficient to induce cell death in cancer cells but caused significantly less toxicity in normal skin and lung cells. This finding is remarkable as the novel FMD compounds seem to exert certain selectivity for cancer cells and essentially act as "targeted" chemotherapy. Previous data have shown evidence that cancer cells may be characterized by a reduced intracellular environment and high levels of antioxidants with weakly bound electrons. Indeed, the authors provide first evidence that treatment with FMD compounds selectively decreased the levels of reduced glutathione (GSH) in cancer cells but increased in normal cells. This data is consistent with the expected DET reaction between FMD compounds and GSH molecules and could explain the selective cytotoxic effect on cancer cells. Whether and to which extent antioxidants and ROS contribute to tumor progression and therapeutic resistance is still a matter of intense research (DeNicola et al., 2011). The observed effects may highly depend on the specific tissue and predisposing genetic and metabolic alterations. Therefore, further investigations are needed in this important field to establish a causative relation between antioxidant levels, ROS status and the amount of intrinsically available weakly bound electrons in cancer cells. This knowledge could then be exploited not only for novel therapeutic approaches but also for potential preventive strategies.

In summary, the paper by Lu et al. presents a fascinating extension of the armamentarium to fight the war against cancer. However, further preclinical evaluation of FMD compounds, preferably in genetically engineered mice or patient-derived xenograft mice (avatars), is needed to set the stage for early clinical trials in cancer patients.

References

DeNicola, G.M., Karreth, F.A., Humpton, T.J., Gopinathan, A., Wei, C., Frese, K., Mangal, D., Yu, K.H., Yeo, C.J., Calhoun, E.S., et al., 2011. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature 475, 106–109.
Hanahan, D., 2014. Rethinking the war on cancer. Lancet 383, 558–563.
Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144, 646–674.
Lu, Q.B., Kalantari, S., Wang, C.R., 2007. Electron transfer reaction mechanism of cisplatin with DNA at the molecular level. Mol. Pharm. 4, 624–628.
Lu, Q.-B., Zhang, Q.-R., Ou, N., Wang, C.-R., Warrington, J., 2015s. In vitro and in vivo studies of non-platinum-based halogenated compounds as potent antitumor agents for natural targeted chemotherapy of cancers. EBio Med. 2, 543–552.
Luengo-Fernandez, R., Leal, J., Gray, A., Sullivan, R., 2013. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol. 14, 1165–1174.
Migus, A., Gauduel, Y., Martin, J.L., Antonetti, A., 1987. Excess electrons in liquid water: First evidence of a prehydrated state with femtosecond lifetime. Phys. Rev. Lett. 58, 1559–1562.
Siegel, R.L., Miller, K.D., Jemal, A., 2015. Cancer statistics, 2015. CA Cancer J. Clin. 65, 5–29.
Wang, C.R., Nguyen, J., Lu, Q.B., 2009. Bond breaks of nucleotides by dissociative electron transfer of nonequilibrium prehydrated electrons: a new molecular mechanism for reductive DNA damage. J. Am. Chem. Soc. 131, 11320–11322.