Documentaţie pentru fizicieni medicali

Radicali liberi

În acest document raportăm o serie de articole ştiinţifice noi, publicate în literatura de specialitate, referitoare la radicalii liberi generaţi prin folosirea radiaţiilor în tehnicile de radioterapie, la substanţe protectoare împotriva radicalilor liberi, mecanismul molecular de acţiune a radicalilor liberi. Aceste articole vor fi puse la dispoziţia studenţilor pe canalele de comunicare on-line (platform Teams, site-ul proiectului).

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Teme

- Substanţe protectoare împotriva radicalilor liberi (free radicals scavengers)
- Folosirea glucozei în dozimetria radiaţiilor
- Mecanismul deteriorării AND-ului de către radiaţiile ionizante şi UV
- Mecanismul molecular şi biodisponibilitatea polifenolilor în cancerul de prostată

Lista articolelor propuse

Articol 1

Claude Le Sech, Ryoichi Hirayama, Dual aspect of radioenhancers and free radical scavengers, Free Radical Biology and Medicine 159 (2020) 103–106, https://doi.org/10.1016/j.freeradbiomed.2020.06.019

Abstract

Combining an external beam of ionizing particles with agents to augment the dose effects of cell damages for therapeutic purpose is an important goal of radiotherapy. This last decade intensive works have focused on metal compounds or metal nanoparticles as radiosensitizers to increase the oxidative damages under irradiation. In principle the nanoparticles can be coated with a functionalized shell, to achieve a specific targeting of the tissues, making such approach attractive. The functionalized coating is made of polymers. These molecules are able to scavenge the free radicals, thus, the coating can decrease the overall efficacy of the radiation. The purpose of the present model is to analyse the role of free hydroxyl radicals in the dual behaviour of the added agent. Consideration of the efficiency of the added agents versus the Linear Energy Transfer - LET - of the ionizing particles is made. It is shown that an efficient agent combined with a low-LET particle beams might become less efficient when high-LET particles like heavy-ions are used. These general considerations should be useful to optimize the design of the nanoparticles to be combined with the different kind of ionizing particles.

Keywords: Radiosensitizers, Nanoparticles, Hydroxyl radical, Free radical scavengers

Concluzii

Conclusion

When applying coating to nanoparticles intended for radiosensitising agents is that the coating may absorb some HO°, decreasing the efficiency. The present work proposed a criterion to optimize the radiosensitisers efficiency combined with ionizing particles at different LET. An agent irradiated with low-LET IPs might become less effective when high-LET IPs are used. We believe that these considerations give a pathway towards the

rational design of potent radiosensitizers, and their usefulness in radiotherapy. It is probably best to introduce radiosensitizers when low-LET radiations considering such as gammas-rays, X-rays, protons or helium-ions. In these conditions, the scavenging rate is expected to be
smaller than their radiosensitizing contribution. A good candidate for any IPs, should by a small molecule, containing a high-Z-atom, with few cytotoxicity or systemic toxicity and a selective metabolic uptake by transformed cells.

Articol 2

A. Belahmar, M. Mikou, A. Mamadou Saidou, R. El Baydaoui, M. Bougteb, EPR study of dosimetric properties of glucose irradiated by X-photons and, electrons: Analyse of storage effect on produced free radicals, Radiation Physics and Chemistry 152 (2018) 6–11 https://doi.org/10.1016/j.radphyschem.2018.07.010

Abstract

Electron Paramagnetic Resonance “EPR” measurements were undertaken on powder glucose irradiated by X photons and electrons in order to study its dosimetric properties and evaluate its spectral behaviour in the field of radiotherapy. Dose-response evolution and the impact of storage on irradiated samples were analysed using peak to peak amplitude and double integration method. The obtained measurable threshold dose is 2 Gy. The dependence of the EPR signal as function of the absorbed dose was found to be linear in the dose range 0 – 20 Gy for all used energies. An effect of the type of radiation on the sensitivity is observed, glucose seems to be slightly more sensitive to X photons irradiation than to electrons. The investigations of shape and intensity of EPR signals during storage period of twelve months revealed a consequent radical activity, probably due to two major free radicals produced by irradiation. The signal height of one of the EPR components increases significantly during the first two months after irradiation, and then stabilizes.

Keywords: Glucose, Electron Paramagnetic Resonance, Radicals, Dosimetry

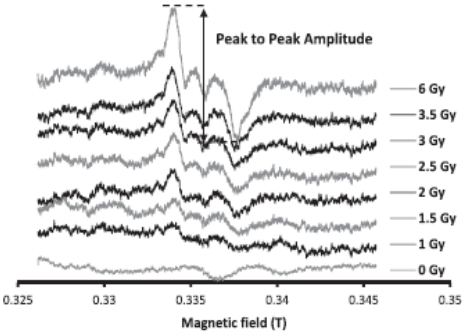


Fig. 1. EPR spectra of glucose irradiated to 6 MV X-ray, recorded with modulation amplitude of 0.5 mT and microwave power of 1 mW.

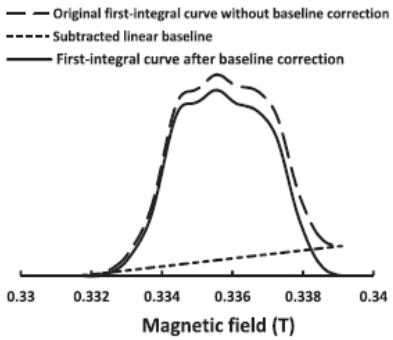


Fig. 2. First-integral curve of a 20 Gy EPR spectrum of glucose before and after baseline correction.

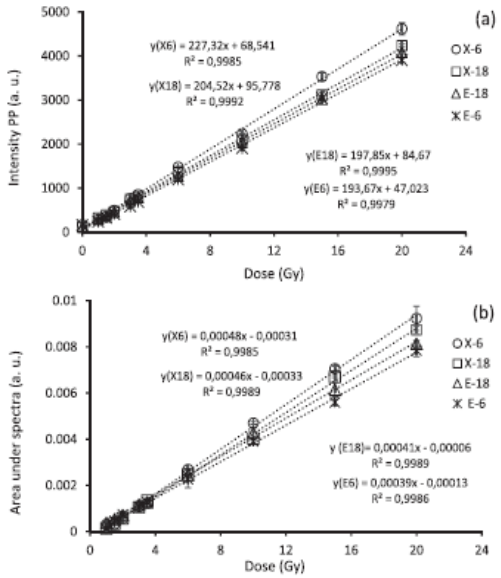


Fig. 3. EPR response of glucose versus absorbed dose measured at the same interval time after irradiation by X-photons and electrons using peak to peak method [a] and double integration method [b].

Concluzii

The obtained results indicate that glucose is able to provide dose measurements starting from 2 Gy. The response of this material gives good linearity in the dose range 2–20 Gy. An effect of the nature of the irradiating particles and energy is observed, the glucose seems to be more sensitive to X photons irradiation than to electrons. This result suggests the establishment of a dosimetry curve for each used particle.

The EPR measurements undertaken during the storage period after irradiation showed a significant radical reactivity undoubtedly due to at least two free radicals produced by irradiation. The concentration of one of these free radicals appears to increase during the first two months after irradiation and then stabilizes. This increase is probably accompanied by the decrease of the concentration of another free radical, based on the

fact that a weak fading of the global EPR signal is observed under the effect of the storage period using double integration method. A deep analysis of the observed fading effect by considering the impact of moisture, light and temperature during storage period may contribute to reduce this effect. It would be interesting to perform deconvolution calculations on the EPR spectrum of irradiated glucose, in order to identify the contributions associated with this spectrum and to analyse separately their evolution as a function of the irradiation dose and the storage time.

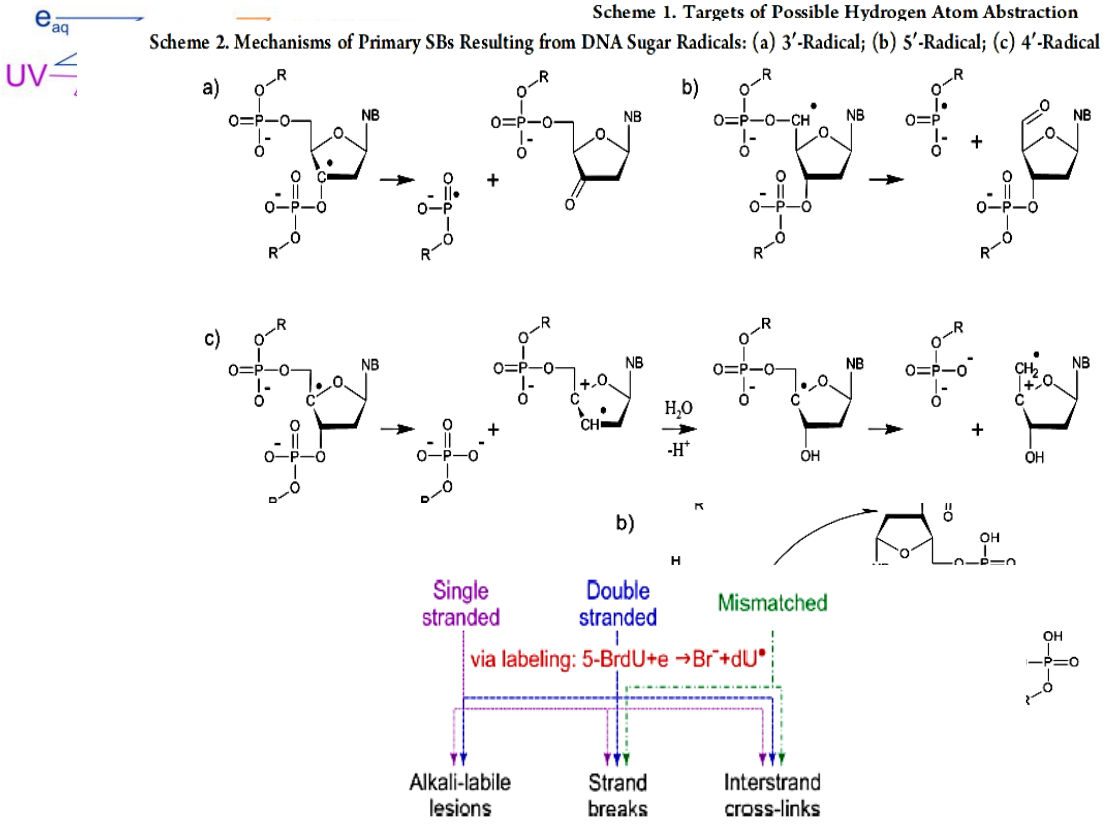
Articol 3

Janusz Rak, Lidia Chomicz, Justyna Wiczk, Kinga Westphal, Magdalena Zdrowowicz, Paweł Wityk, Michał Żyndul, Samanta Makurat, Łukasz Golon, Mechanisms of damage to DNA labeled with electrophilic nucleobases induced by ionizing or UV radiation, J. Phys. Chem. B 2015, 119, 8227–8238, doi: https://doi.org/10.1021/acs.jpcb.5b03948

Abstract

Hypoxia - a hallmark of solid tumors - makes hypoxic cells radioresistant. On the other hand, DNA, the main target of anticancer therapy, is not sensitive to the near UV photons and hydrated electrons, one of the major products of water radiolysis under hypoxic conditions. A possible way to overcome these obstacles to the efficient radio- and photodynamic therapy of cancer is to sensitize the cellular DNA to electrons and/or ultraviolet radiation. While incorporated into genomic DNA, modified nucleosides, 5-bromo-2′- deoxyuridine in particular, sensitize cells to both near-ultraviolet photons and γ rays. It is believed that, in both sensitization modes, the reactive nucleobase radical is formed as a primary product which swiftly stabilizes, leading to serious DNA damage, like strand breaks or cross-links. However, despite the apparent similarity, such radio- and photosensitization of DNA seems to be ruled by fundamentally different mechanisms. In this review, we demonstrate that the most important factors deciding on radiodamage to the labeled DNA are (i) the electron affinity (EA) of modified nucleoside (mNZ), (ii) the local surroundings of the label that significantly influences the EA of mNZ, and (iii) the

strength of the chemical bond holding together the substituent and a nucleobase. On the other hand, we show that the UV damage to sensitized DNA is governed by long-range photoinduced electron transfer, the efficiency of which is controlled by local DNA sequences. A critical review of the literature mechanisms concerning both types of damage to the labeled biopolymer is presented. Ultimately, the perspectives of studies on DNA sensitization in the context of cancer therapy are discussed.



Scheme 1. Targets of Possible Hydrogen Atom Abstraction

Scheme 2. Mechanisms of Primary SBs Resulting from DNA Sugar Radicals: (a) 3′-Radical; (b) 5′-Radical; (c) 4′-Radical

Figure 1. Main degradation pathways for 5-BrdU-labeled single-stranded, double-stranded, and mismatched DNA. Adapted with permission from ref 57. Copyright 2009 American Chemical Society.

Concluzii

Electrophilic nucleosides, especially brominated ones, make labeled DNA sensitive to solvated electrons and UV photons, i.e., to physical factors to which the native DNA is insensitive. These findings open a route by which to employ such electrophilic nucleosides in radiotherapy and the photodynamic therapy of solid cancer. In this Mini-

Review Article, the current status of studies concerning the reactivity of modified nucleosides in DNA context toward excess electrons and near UV photons is summarized. Although the mechanisms responsible for the ionizing radiation-induced and photoinduced damage to DNA are quite different, the ultimate outcome of the γ and photo irradiation of labeled DNA is similar. Namely, the major lesions observed are strand breaks, cross-links, and abasic sites. The similarity of ultimate products triggered by electrons and photons is related to the formation of radicals localized to nucleobases in both reaction pathways. These neutral radicals originate from nucleobase radical anions easily releasing an anionic substituent. The radical anions of modified nucleobases occurring in the radiolysis form as a result of electron attachment to the modified nucleosides which play the role of an electron trap in DNA. Therefore, the yield of this process should be correlated with the ease by which mNZ undergoes DEA and its electron affinity, which depends on the local DNA sequence. On the other hand, photoinduced strand breaks, which belong to the most efficient type of photodamage, are governed by long-range electron transfer from a distant guanine and, therefore, are also sequence-dependent.

The present rather deep comprehension of the mechanisms lying behind the radiation and photoinduced damage to the DNA labeled with electrophilic nucleosides makes the rational design of new, more potent than 5-BrdU, modified nucleosides possible. Currently, we are studying the sensitizing features of 5- SCNdU and 5-OCNdU - mNZs - that we proposed quite recently using molecular modeling which employed the knowledge on DNA radiosensitization by the substituted uracil. A therapeutically valuable compound should not only be a potent DNA sensitizer but also has to be efficiently phosphorylated in the cell and then accepted by human polymerases during DNA biosynthesis. Therefore, before animal tests and clinical trials, any promising mNZ has to be hecked in silico, both as a damaging agent and as a substrate for kinases and polymerases, then synthesized, tested in model radiationchemical and photochemical studies, introduced to cancer cells, and ultimately tested under the destined conditions. Only the mNZs that passed this interdisciplinary and quite complex evaluation procedure could be employed in future anticancer therapies.

Articol 4

1. Teodora Costea, Péter Nagy, Constanta Ganea, János Szöllosi, Maria-Magdalena Mocanu

Molecular Mechanisms and Bioavailability of Polyphenols in Prostate Cancer

Int. J. Mol. Sci. 2019, 20, 1062; doi:10.3390/ijms20051062

Abstract

Abstract: Prostate cancer is the one of the most frequently diagnosed cancers among men over the age of 50. Several lines of evidence support the observation that polyphenols have preventive and therapeutic effects in prostate cancer. Moreover, prostate cancer is ideal for chemoprevention due to its long latency. We propose here an equilibrated lifestyle with a diet rich in polyphenols as prophylactic attempts to slow down the progression of localized prostate cancer or prevent the occurrence of the disease. In this review, we will first summarize the molecular mechanisms of polyphenols in prostate cancer with a focus on the antioxidant and pro-oxidant effects, androgen receptors (AR), key molecules involved in AR signaling and their transactivation pathways, cell cycle, apoptosis, angiogenesis, metastasis, genetic aspects, and epigenetic mechanisms. The relevance of the molecular mechanisms is discussed in light of current bioavailability data regarding the activity of polyphenols in prostate cancer. We also highlight strategies for improving the bioavailability of polyphenols. We hope that this review will lead to further research regarding the bioavailability and the role of polyphenols in prostate cancer prevention and treatment.

Keywords: dietary polyphenols; bioavailability; molecular mechanisms; prostate cancer

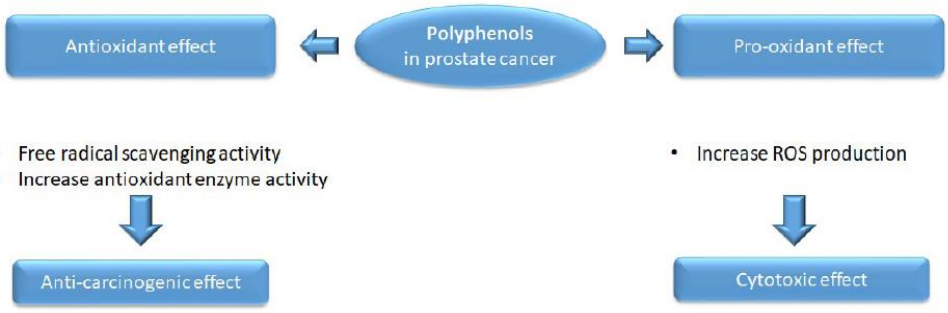
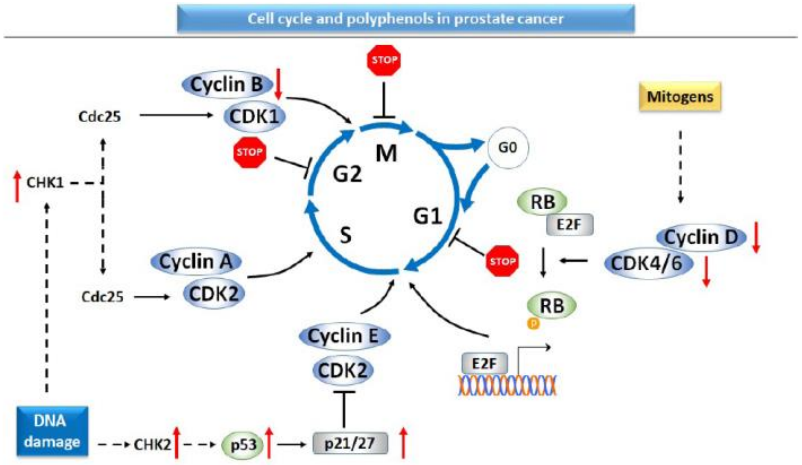


Figure 1. Antioxidant and pro-oxidant effects of polyphenols in prostate cancer. Polyphenols can act as both antioxidant molecules, by free radical scavenging, and as pro-oxidant agents, by increasing ROS production—the mechanisms are dependent on the concentrations applied. In addition, polyphenols are able to increase the level of antioxidant enzymes in prostate cancer cell lines or in animal models of prostate cancer.



Concluzii

Conclusions

Polyphenols act as chemopreventive agents in prostate cancer due to their antioxidant or pro-oxidant effects (through reduction of ROS, increasing antioxidant enzyme activity, or inducing cytotoxicity), modulation of androgen receptors (inhibition of expression and function) or their transactivation of signaling pathways (PI3K, Akt, ERK1/2, FoxO, GSK-3_, RTK, etc). Furthermore, they induce cell cycle arrest (through downregulation of cyclin D1, cyclin E, CDK2, CDK4, and cdc25 and upregulation of proteins coded by tumor suppressor genes such as p53, p21, p27, etc.) and apoptosis (through activation of

caspase-3, caspase-9, cytochrome c, or Bax proteins). Moreover, polyphenols have proven beneficial against tumor invasion through inhibition of angiogenesis and metastasis. The decline of metastatic tumors is due to a reduction in enzymes such as MMPs and uPA and an increase in E-cadherin, while the inhibition of angiogenesis is the consequence of reduced levels of VEGF. The main epigenetic mechanisms responsible for the antitumor effects of polyphenols involve a decrease in the hypermethylation of tumor suppressor genes and downregulation of oncogenic miRNA.

The role of polyphenols in both the treatment and prevention of prostate cancer depends on their bioavailability. Oral bioavailability was shown to be variable depending on the chemical structure of each compound, food matrix, interaction with other nutrients, and host-related factors. Interestingly, polyphenol metabolites, such as urolithins, equol, enterodiol, enterolactone, protocatechuic acid, 3-hydroxyphenyl propionic acid, 4-hydroxyphenylacetic acid, and hippuric acid play an important role against prostate cancer. However, most of the studies conclude that polyphenol bioavailability is relatively low. Therefore, the development of new strategies to enhance their bioavailability is a subject of present interest. A promising approach in this regard is the development of drug delivery systems that are able to release polyphenols in a controlled manner and in the target tissue. Other methods for increasing the bioavailability of polyphenols include solid dispersion techniques for microencapsulation, de novo formulations, or alternative routes of administration. Better knowledge about the bioavailability of polyphenols is essential to properly evaluate their role as chemopreventive agents in different types of cancer, and continuous research in this area is needed.