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INFLUENCE OF REDOX CYCLERS ON THIOL OXIDATION IN THE PRESENCE OF NANOPARTICLES

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Background: An increase in metabolic rate interconnected with oxidative imbalance are major features of tumor process. Higher ROS (reactive oxygen species) levels make tumor cells more sensitive to oxidative stress compared to normal cells. Therefore, generating additional ROS can lead to cancer cell death. Redox cycling is a crucial process responsible for the production of ROS by various clinical and experimental anticancer agents. Among these compounds are quinones and ascorbic acid, which exhibits a synergistic antitumor effect. Elevated glutathione levels and glutathione-dependent antioxidant enzymes play a key role in protecting cancer cells from intracellular oxidative stress. Nanoparticles with glutathione depletion properties can act as smart chemodynamic agents, disrupting the cellular antioxidant defense system. In this work, inorganic nanoparticles based on rare earth elements are used as catalytic amplifiers of one-electron transfer with the formation of organic and oxygen radicals in the redox cycles of ascorbic acid and vitamin K3.

Objectives: The thiol oxidation was studied in the presence of nanoparticles in combination with redox cyclers.

Materials and methods: As an indicator of the pro-oxidant efficiency of nanoparticles (CeO_2 (2 nm, 20 μg/ml) or $GdYVO_4:Eu^{3+}$ (2 nm, 20 μg/ml)) combined with organic compounds (ascorbic acid (100 or 200 μM) and vitamin K3 (4 μM)) changes in the level of thiols (glutathione (200 μM), L-cysteine (200 μM) or dithiothreitol (500 μM)) in the model system were used.

Results: It was shown that $GdYVO_4:Eu^{3+}$ and CeO_2 nanoparticles enhances oxidation of thiols under an influence of the redox active molecule as well as their combination. The efficiency of bare nanoceria as well as in redox cyclers combinations was higher compared to respective orthovanadate nanoparticles combinations (including time dynamics) that was especially pronounced in the dithiothreitol oxidation system.

Conclusions: The data obtained indicate the ability of nanoceria to significantly enhance the oxidation of thiols induced by redox cyclers revealing the perspective of this approach in solving the problem of increased thiol level in tumor cells.

KEY WORDS: CeO_2 nanoparticles; $GdYVO_4:Eu^{3+}$ nanoparticles; thiols; ascorbic acid; tumor cells.

In tumor cells increase in metabolic rate, cellular signaling processes, and activity of antioxidant enzymes caused by ROS (reactive oxygen species) have been reported. Higher ROS

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level in tumor cells makes them more ROS-sensitive than normal cells. So, additional ROS generation can cause cancer cell death with negligible effect on non-tumor cells [1]. Although ROS-generating agents have been found to be effective in many cases, low clinical response and resistance to those agents were also reported. Elevation of certain transcription factors, antioxidants and survival signals as a result of redox adaptation probably explains the drug resistant phenotype [2, 3].

Elevated levels of glutathione (GSH), a major intracellular redox buffer, and GSH-dependent antioxidant enzymes play a central role in protection of cancer cells against intracellular oxidative stress [4]. This fact can be one of the most sufficient obstacles for cancer treatment. High levels of GSH have been found in various tumor types being up to several-fold more than in surrounding tissues. The overexpression of GSH in tumors indicates enhanced cell proliferation, decreased levels of apoptosis, increased resistance to chemotherapeutic drugs and radiation therapy.

Development of effective therapeutic agents, which are selective and able to overcome drug resistance, requires reconsideration of the concepts of intrinsic oxidative stress in cancer cells and their redox adaptation [2].

Redox cycling is an important chemical mechanism underlying formation of ROS by numerous clinical and experimental anticancer agents containing quinone pharmacophores (including anthracyclines, geldanamycin, and menadione) [5]. The redox cycling induced toxicity of quinones (Q) was largely investigated. The molecular mechanism is believed to be that the semiquinone radical is generated by spontaneous or enzyme-catalyzed reduction of Q in the cell. The semiquinone radical is oxidized by oxygen with formation of parent Q and superoxide radical. NAD(P)H and GSH systems are implicated in the process. So, enzymatic or non-enzymatic reduction of menadione converts it from pro-drug to drug compound with antitumor activity [1]. However, the systemic toxicity of menadione, a short half-life and low concentration (only 7.4 μM in plasma) make it difficult to use as a monotherapy. Its use in various combinations (with vitamin C (AA), orthovanadates (OV, $GdYVO_4:Eu^{3+}$ NPs)) is considered more promising [6]. A recent study has shown the potent anticancer activity of menadione and ascorbate combination due to induced redox cycling [7].

Nanoparticles (NPs), with GSH depletion properties can serve as a smart chemodynamic agent disrupting the cellular antioxidant defense system. Drug development based on multifunctional redox catalysts that selectively enhance oxidative stress in cancer cells through GSH depletion, ROS formation, and thiol oxidation in crucial redox target proteins including transcription factors has been initiated. Prooxidant and antioxidant redox effects as a function of cellular redox status and GSH availability, provide a therapeutic window based on cancer cell redox dysregulation with elevated peroxide and decreased GSH cellular levels.

It has been shown that artificial enzymes mimic the activity of peroxidases, oxidases, superoxide dismutase, and hydrolases, while limited data are available regarding reductase mimetics [8]. It has been suggested that NPs with oxidoreductase activity can function as redox cycling activators or mediators and catalysts facilitating interactions and electron transfer between organic compounds. Since these processes can involve thiol compounds or reducing equivalents, this fact leads to their consumption and a decrease in the overall reductive activity in the system and an increase in prooxidant potential.

Prooxidant effect of GSH depletion by orthovanadate NPs has been demonstrated previously [9]. It was also found that cerium dioxide NPs exhibit GSH and cysteine oxidation activities [10, 11]. The antitumor activity of nanoceria and orthovanadate NPs is also known [12, 13]. However, the mechanism of these effects remains poorly understood.

In the present study, thiol oxidation system was used to evaluate the combined prooxidant efficacy of vitamin K3 and AA in the presence of extra-small (2 nm) orthovanadate and cerium dioxide NPs.

MATERIALS AND METHODS

Reagents: vitamin C (Thermo Fisher Scientific, USA), glutathione (AppliChem GmbH, Germany), L-cysteine (Sigma–Aldrich, USA), dithiothreitol (Merck KGaA, Germany); Tris-buffer (AppliChem GmbH, Germany), vitamin K3 (MSB, Darnytsia, Ukraine), 5`5`-dithio-bis(2-nitrobenzoic) acid (Sigma-Aldrich, USA).

Colloidal solutions of CeO_2 and $GdYVO_4:Eu^{3+}$ NPs were obtained and characterized as described previously [14, 15]. Transmission electron microscope (TEM) images of each sample were collected using a TEM 125K (Selmi) transmission electron microscope (100 kV). According to the TEM, solid phase of colloidal solution consists of $GdYVO_4:Eu^{3+}$ spherical NPs with average sizes of 2 nm and CeO_2 NPs with average sizes of 2 nm.

Dynamic light scattering was used to reveal the hydrodynamic diameter of the NPs (CeO_2 (9 nm) and $GdYVO_4:Eu^{3+}$ (26.8 nm)) using a ZetaPALS analyzer (Brookhaven, NY) equipped with He−Ne laser (658 nm). Measurements of zeta potential were conducted using a ZetaPAls/bi-masanalyzer (Brookhaven Instruments Corp., USA), operating in phase analysis light scattering mode. The experiments were performed at a scattering angle of 90° and λ = 659 nm, at a temperature of 25 °C. The zeta potential was obtained through measurement of the electrophoretic mobility of the particles which was converted to apparent zeta-potentials using the Helmholtz-Smoluchowski relationship. For each test, at least ten records were obtained and averaged. Notably, the zeta potential was found to be negative.

Oxidative potential (OP) is most common measure of the ability to oxidize target molecules. These molecules include low molecular weight natural antioxidants such as AA, monothiols (GSH, L-cysteine), dithiols (dithiothreitol (DTT)) [16, 17]. Our studies assessed the oxidation of mono- and dithiols both under the influence of NPs (cerium dioxide and orthovanadates) and their combinations with redox cyclers [5, 18]. The oxidation of GSH, L - cysteine and DTT was monitored by spectroscopic techniques using Specord 200 spectrophotometer (Analytik Jena, Germany). Suspensions of NPs (CeO_2 (2 nm, 20 μg/ml) or $GdYVO_4:Eu^{3+}$ (2 nm, 20 μg/ml) in 10 mM Tris HCl buffer combined with organic compounds (AA (100 or 200 μM), vitamin K3 (Q) (4 μM)) changes in the level of thiols (GSH (200 μM), L-cysteine (200 μM) or DTT (500 μM)) in the model system were used. The pH dependence (pH 6.7, 7.4, 7.8) and time dynamics of the process within 24 hours were studied. The rate of thiol oxidation was evaluated by measuring the disappearance of –SH groups. Free –SH groups were determined according to [19]. Incubation at 37 ºC was initiated by the addition of the thiol compounds. Aliquots of the reaction mixture (100 μL) were checked for the amount of –SH groups using absorbance at 412 nm at different times after addition of 5`5`-dithio-bis(2-nitrobenzoic) acid (DTNB) color reagent. Adding DTNB to the mixtures yielded a yellow product (forms 2-nitro-5-thiobenzoic acid (TNB)), which is stable in the final solution for at least 2 hours at room temperature. TNB content was determined by spectroscopic techniques using Specord 200 spectrophotometer from absorbance at 412 nm with solution of thiols without NPs used as a control. The level of thiols was expressed as relative change (as a reference the absorbance value at 0 hours was taken). For statistical analysis Origin software was used. Deviations were analyzed by Shapiro-Wilk test. Subsequent analysis included one-way ANOVA with Dunn-Sidak post-hoc test or Kruskal-Wallis ANOVA with Mann-Whitney post-hoc test. The values were expressed as mean ± SEM from 3 to 5 independent experiments performed in duplicate, and the results were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Low molecular weight thiols are present in high concentrations in most cells. Modification of cysteinyl residues can impart or regulate molecular functions important to cellular processes including signal transduction. In addition, in connection with the mentioned above thiol-dependent mechanism of tumor resistance, prooxidant effect of NPs in relation to thiols should be studied. There are evidences that redox action of nanoceria induces the formation of disulfide bridges in thiol-containing biomolecules [11].

We have shown that reduced GSH is the most resistant to oxidation by NPs of all the thiols studied in this work. With CeO_2 NPs as well as combining CeO_2 NPs with recyclers, significant decrease in the level of reduced GSH was noted. However, the drop in its level occurs only at sufficiently long incubation (24 hours) and only in a neutral and slightly alkaline environment (Fig. 1). Unlike nanoceria, orthovanadate NPs revealed such properties only at pH 7.8 when combining with AA.

During the oxidation of L-cysteine, much more pronounced and early effect of nanoceria was observed (Fig. 2).

In contrast to GSH oxidation, the opposite pH dependence along with different dynamics was observed during L-cysteine oxidation in the presence of CeO_2 NPs. Thus, already within 6 hours of incubation, the process was accelerated with the most pronounced effect at slightly acidic pH values with 0.238 ± 0.046 r.u, 0.317 ± 0.044 r.u., and 0.363 ± 0.076 r.u. (relative to the value at $t = 0$ hours) for pH 6.7, 7.4, and 7.8, respectively.

Under neutral conditions, at pH 7.4, a significant drop in the –SH groups of L-cysteine occurred after only 6 hours of incubation with nanoceria. However, in contrast to the process of GSH oxidation, the addition of AA inhibited the pro-oxidant effect of nanoceria at the initial stage of the experiment, which was especially noticeable with increasing concentration of AA. By 24 hours of incubation, the effect of all combinations of redox compounds with nanoceria was observed leading to almost complete oxidation of the thiol groups of L-cysteine. The effect of orthovanadate NPs on this indicator did not differ from the appropriate time control and did not change the effects of redox compounds. The most striking prooxidant effect of nanoceria on thiols when interacting with redox cyclers was found in a system containing DTT (Fig. 3).

As can be seen from the Fig. 3, the dynamics of DTT oxidation by nanoceria and orthovanadates differ. Delay of prooxidant effect by 24 hours for combinations of orthovanadate NPs with Q compared to the same effect for combination of nanoceria with Q was observed.

So, for all studied thiols the oxidation activity of nanoceria predominates, while orthovanadate NPs and their combinations were rather neutral. It also should be noted that in the absence of NPs additive effect of redox molecules was most clearly manifested for DTT oxidation, in Cys-based system it was weaker and absent in GSH-based system.

Extra-small CeO_2 (2 nm) NPs are not only capable of exhibiting a prooxidant effect to GSH even at neutral pH, which is consistent with previously obtained results [10], but also enhance the oxidation of other thiols. In contrast to nanoceria, extra-small $GdYVO_4:Eu^{3+}$ (2nm) NPs did not exhibit a similar effect, neither to GSH (in accordance to our previous results [10]), nor to other studied thiols. However, in some cases, orthovanadate NPs exhibited prooxidant effect when combined with redox cyclers. At the same time, the effect of nanoceria and its combinations with redox compounds was more pronounced. This is especially true for combinations with the both — AA and vitamin K3 (a combination that has attracted the increased attention of oncology specialists for quite a long time and have shown high antitumor efficacy both in vitro and in vivo [20–22].

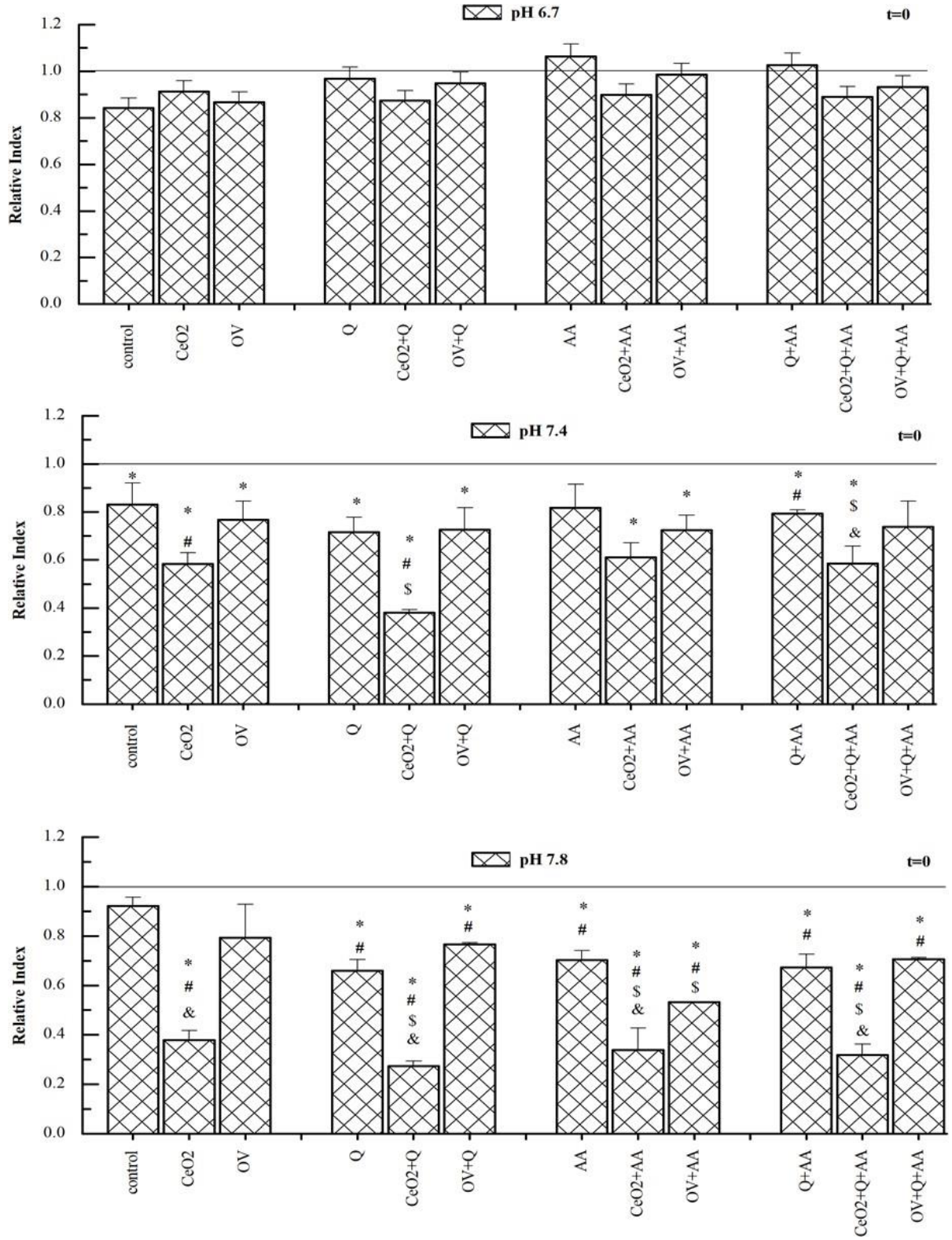

Fig. 1. Oxidation of GSH under an influence of CeO_2 and $GdYVO_4:Eu^{3+}$ (OV) NPs within 24 hours at 37 ºC and pH 6.7, 7.4, and 7.8 in the presence of 100 μM AA and vitamin K3 (Q) in different combinations.
Note:
* – significant differences compared to initial control t = 0, $p < 0.05$;
# – significant differences compared to appropriate 24 hours control, $p < 0.05$;
$ – significant differences compared to appropriate compound control, $p < 0.05$;
& – significant differences between CeO_2 NPs-based and $GdYVO_4:Eu^{3+}$ (OV) NPs-based combination, $p < 0.05$.

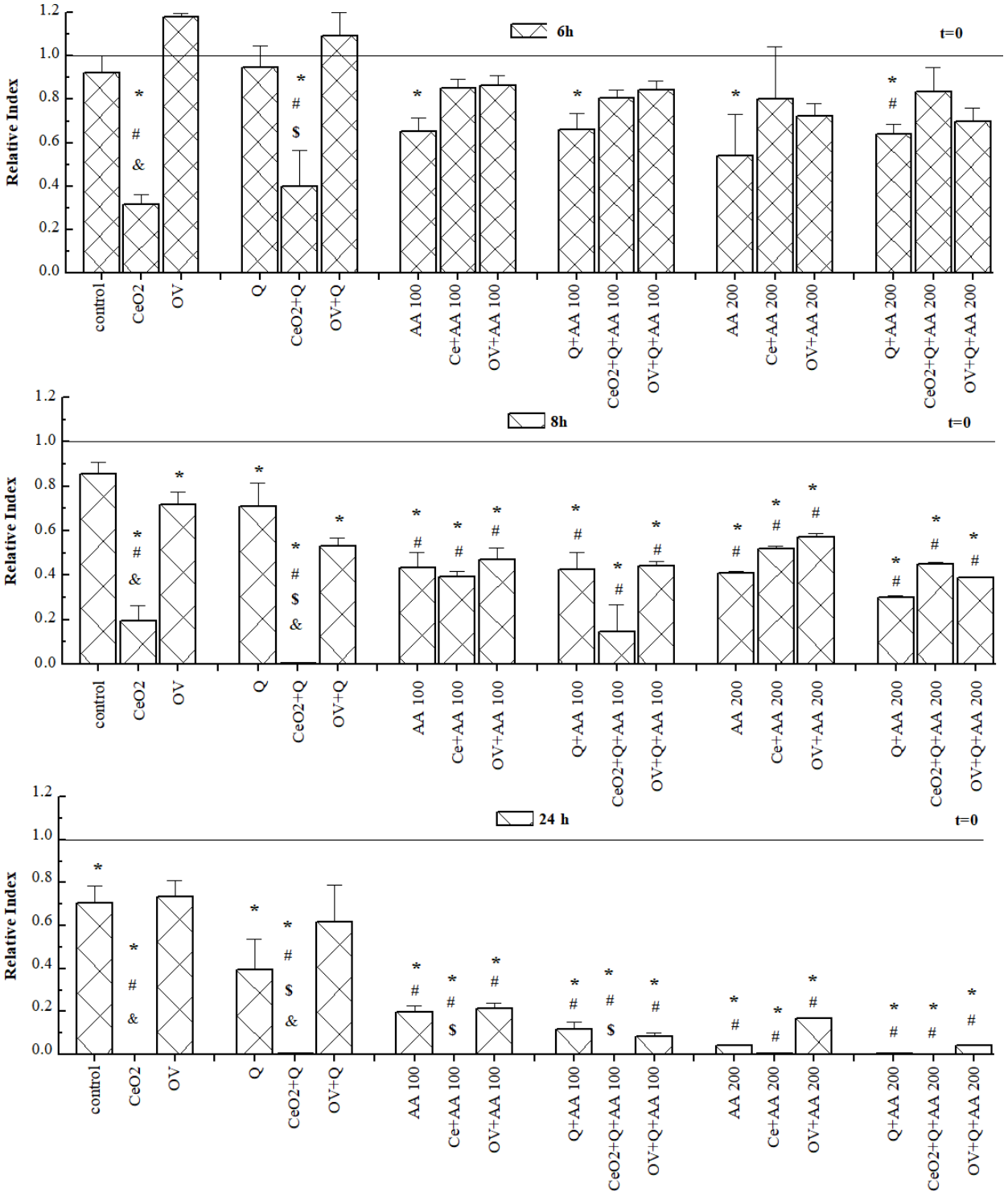

Fig. 2. Dynamics of oxidation of L-cysteine at 37 °C at pH 7.4 under the influence of CeO_2 and $GdYVO_4:Eu^{3+}$ (OV) NPs at pH 7.4 in the presence of 100 or 200 μM AA and vitamin K3 (Q) in different combinations.

Note:

* – significant differences compared to initial control t = 0, $p < 0.05$;

– significant differences compared to appropriate time control, $p < 0.05$;

$ – significant differences compared to appropriate compound control, $p < 0.05$;

& – significant differences between CeO_2 NPs-based and $GdYVO_4:Eu^{3+}$ (OV) NPs-based combinations, $p < 0.05$.

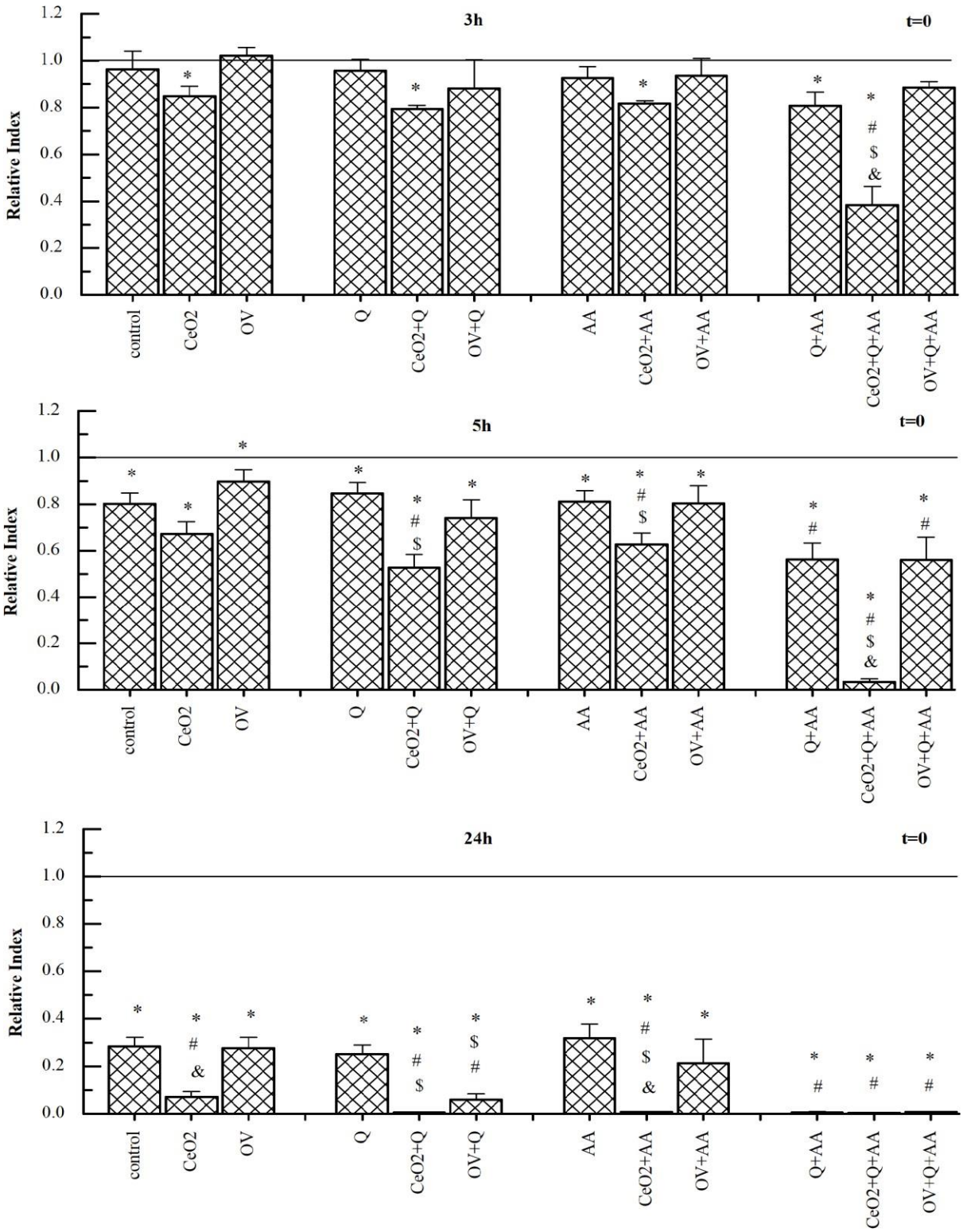

Fig. 3. Dynamics of oxidation of DTT under the influence of CeO_2 and $GdYVO_4:Eu^{3+}$ (OV) NPs at pH 7.4 in the presence of 100 μM AA and vitamin K3 (Q) in different combinations.
Note:
* – significant differences compared to initial control t = 0, $p < 0.05$;
# – significant differences compared to appropriate time control, $p < 0.05$;
$ – significant differences compared to appropriate compound control, $p < 0.05$;
& – significant differences between CeO_2 NPs-based and $GdYVO_4:Eu^{3+}$ (OV) NPs-based combinations, $p < 0.05$.

It can be assumed that the oxidation of thiols (as well as other low-molecular antioxidants) due to the oxidase activity of nanoceria can represent one of the specific and leading mechanisms in the disruption of the functioning of antioxidant systems of tumor cells. The increase in the oxidase-like activity of nanoceria with pH decrease, should enhance the prooxidant effect of nanoceria, on tumor cells (also evidenced by a number of studies [23, 24]), which being combined with redox cyclers, can contribute to decrease in the effectiveness of protective systems (based on low-molecular antioxidants) and thiol-dependent signaling systems of tumors stimulating the destruction of tumor cells.

At the same time, the results obtained in the work did not allow us to draw an unambiguous conclusion about an involvement of pH-dependent oxidase-like activity of nanoceria in the direct oxidation of natural monothiols. Indeed, an increase in the prooxidant properties of NPs (first of all, of nanoceria) with pH decrease enhanced by the presence of redox cyclers is well known. However, in the thiol-containing model system, the pH dependence is not so straightforward. On the one hand, the literature data on higher stability of GSH in more acidic environment are verified. We have shown an increase in GSH oxidation with pH increase only during prolonged incubation (24 hours), which indicates high thiol stability. However, in the cysteine-containing system, faster thiol oxidation (within 6 hours) and opposite pH dependence of CeO_2 NPs prooxidant effect (with slight increase for weakly-acidic pH) was detected. Differences in the results obtained for different thiols can be explained both by steric effects and possible difference in the values of the dissociation constants of sulfhydryl groups: pKa = 8.36 for L-cysteine, and 9.2 for GSH. In addition, although there are data on the oxidase activity of vanadium NPs in relation to GSH [25], as well as on the binding and oxidation of sulfhydryl groups on the surface of nanoceria [11], these thiols are not convenient substrates for the oxidase-like reaction of the NPs. At the same time, easily autooxidizable substances such as AA or polyphenols capable of forming mono- and bidentate bonds on the surface of NPs [26] can be oxidized via the oxidase-like mechanism not only at acidic ~ pH 5, but also at slightly acidic and neutral pH [27, 28] that can indirectly trigger the response of the thiol disulfide system in cells.

CONCLUSIONS

Thus, the results obtained are consistent with our earlier data on the ability of nanoceria to oxidize low molecular weight antioxidants, including AA, NADPH, and GSH [10]. In this work, a more detailed analysis of the prooxidant effect of cerium dioxide NPs in comparison with orthovanadate NPs in relation to mono- and dithiols was carried out. The pro-oxidant effect of nanoceria was detected for all the studied thiols; GSH demonstrated the highest stability, and for DTT the combined pro-oxidant effect of nanoceria with redox cyclers was most pronounced.

A study of L-cysteine oxidation confirmed higher prooxidant activity of nanoceria and nanoceria-based combinations with redox cyclers in comparison with orthovanadate-based ones. In addition, a slight increase of CeO_2 NPs prooxidant effect in weakly-acidic pH was detected. In this system the combination of nanoceria with Q demonstrated the highest effectiveness. Though the presence of AA in the system reduced the cysteine oxidation efficiency of nanoceria on the early stages of the process, but an increase of pro-oxidant effect was found for all CeO_2-based combinations for 24 hours of incubation. Prooxidant effects of orthovanadate NPs in combination with redox cyclers are delayed and observed only at the late stages of the experiment.

Although in the current model we were not able to show a pronounced pH-dependent enhancement of the oxidative effect of nanoceria, with respect to thiols, it is not excluded that NPs and their combinations with redox cyclers can influence GSH pathways in cancer cells involving other cytotoxicity mechanisms, which require further investigation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ВПЛИВ РЕДОКС-АКТИВНИХ МОЛЕКУЛ НА ОКИСНЕННЯ ТІОЛІВ У ПРИСУТНОСТІ НАНОЧАСТИНОК

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Актуальність. Високі рівні АФК (активних форм кисню) пухлинних клітин роблять їх більш чутливими до окислювального стресу порівняно з нормальними клітинами. Таким чином, утворення додаткових АФК може призвести до загибелі ракових клітин. Окислювально-відновний цикл є ключовим процесом, відповідальним за виробництво АФК різними медичними та експериментальними протипухлинними агентами. Серед цих сполук — хінони та аскорбінова кислота, яка виявляє синергічний протипухлинний ефект. Підвищені рівні глутатіону та

глутатіонзалежні антиоксидантні ферменти відіграють ключову роль у захисті ракових клітин від внутрішньоклітинного окисного стресу. Наночастинки зі властивостями виснаження глутатіону можуть діяти як інтелектуальні хіміодинамічні агенти, які порушують систему антиоксидантного захисту клітин. У даній роботі неорганічні наночастинки на основі рідкоземельних елементів використовуються як каталітичні підсилювачі одноелектронного переносу з утворенням органічних і кисневих радикалів в окисно-відновних циклах аскорбінової кислоти та вітаміну К3.

Мета роботи. Вивчити динаміку окиснення тіолів у присутності наночастинок у поєднанні з редокс-активними молекулами.

Матеріали та методи. Як індикатор прооксидантної ефективності наночастинок (CeO_2 (2 нм, 20 мкг/мл) або $GdYVO_4:Eu^{3+}$ (2 нм, 20 мкг/мл)) у поєднанні з органічними сполуками (аскорбінова кислота (100 або 200 мкМ) та вітамін К3 (4 мкМ)) використовували зміни рівня тіолів (глутатіону (200 мкМ), L-цистеїну (200 мкМ) або дитіотреїтолу (500 мкМ)) у модельній системі.

Результати. Показано, що наночастинки $GdYVO_4:Eu^{3+}$ та CeO_2 підсилюють окиснення тіолів під впливом кожної редокс-активної молекули, а також їх комбінації. Ефективність наноцерію, а також комбінацій редокс-активних молекул, була вищою порівняно з відповідними комбінаціями наночастинок ортованадату (включаючи часову динаміку), що було особливо виражено в системі окиснення дитіотреїтолу.

Висновки. Отримані дані свідчать про здатність наноцерію суттєво посилювати окиснення тіолів, індуковане редокс-активними молекулами, що розкриває перспективність цього підходу у вирішенні проблеми підвищеного рівня тіолів у пухлинних клітинах.

КЛЮЧОВІ СЛОВА: наночастинки CeO_2; наночастинки $GdYVO_4:Eu^{3+}$; тіоли; аскорбінова кислота; пухлинні клітини.