Exp Oncol 2004
26, 2, 140–144

Experimental ONCOLOGY

SELECTIVITY OF EFFECTS OF REDOX–ACTIVE COBALT(III) COMPLEXES ON TUMOR TISSUE

Sergey Osinsky[1,], Ilia Levitin[2], Larissa Bubnovskaya[1], Andrey Sigan[2], Irina Ganusevich[1], Antonina Kovelskaya[1], Natalya Valkovskaya[1], Luigi Campanella[3], Peter Wardman[4]*

[1]*R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of National Academy of Sciences, Kiev, Ukraine*

[2]*A.N. Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences, Moscow, Russia*

[3]*University "La Sapienza", Rome, Italy*

[4]*Gray Cancer Institute, Northwood, UK*

***Aim*: To estimate the selectivity of action of cobalt complexes on tumor tissue. *Materials and Methods*: Cobalt(III) complexes containing both the tetradentate Schiff-base ligand derived from acetylacetone and ethylenediamine, and compounds of the vitamin PP series or their synthetic analogs, viz. nicotinamide, isonicotinamide or nicotinic acid, as extra (axial) ligands, were tested *in vivo* on transplanted mice tumors, namely Lewis lung carcinoma (3LL), melanoma B16, and mammary adenocarcinoma Ca755. Concentrations of malondialdehyde in tissue extracts were measured by standard biochemical methods. The rate of DNA unwinding was used to detect DNA damage in tumor cells. Level of tumor hypoxia as well as bioenergetic status were estimated using ^{31}P NMR spectroscopy in perchloric acid extracts of tissue. *Results*: A significant and selective increase of malondialdehyde in tumor tissue reflecting activation of lipid peroxidation was found after administration of the complexes. The bioenergetic status in tumor was also selectively affected by the complexes: minimization of signals of high-energy phosphates was observed two hours after injection of the complexes. An increase of the number of DNA single-strand breaks was registered in tumor tissue, supporting the suggestion that the complexes may directly affect DNA. A correlation between the above tumor effects and the structure of axial ligands was demonstrated. Conclusion: Cobalt(III) complexes affect tumor tissue with a very high level of selectivity; in particular they activate lipid peroxidation, induce DNA single-strand breaks, suppress the bioenergetic status, and enhance hypoxia. It is supposed that the selective action of these complexes on tumor tissue is due to peculiarities of tumor microphysiology, in particular significant tumor hypoxia.**

***Key Words*: cobalt complexes, redox, tumor hypoxia, selectivity, reactive oxygen species.**

The main goal of cancer therapy is to attain maximum therapeutic gain, i.e. maximum damage of tumor cells in combination with minimum damage to normal cells. This can be achieved in principle via selective antitumor preparations, the cytostatic effects of which would be restricted within tumor tissue. While 100% selectivity may be impractical, achievement of reasonably high selectivity seems to be a feasible aim.

One approach to identification of selective cytostatics is based on the difference in characteristics between malignant and normal tissue, especially in the level of oxygen tension. Thus tumor tissues are known to feature low oxygen tensions or, in other terms, they are characterized by a high hypoxic fraction [1, 2]. The latter condition is a prerequisite for development of so–called bioreductive agents which are activated under hypoxia, yielding active metabolites capable of killing tumor cells [3, 4]. One of such agents, tirapazamine, entered phases II–III of clinical trials quite successfully [5].

In this connection, we are interested in transition metal complexes, the antitumor activities of which have been of potential interest in tumor chemotherapy since the discovery of cytostatic effects of platinum complexes. In particular, complexes of cobalt(III) seem to offer promise due to a high electron affinity of the metal in the trivalent state, ability to bind to DNA and, last but not least, the ready reducibility of the compounds in question [6]. A communication [7] that some cobalt–containing substances are accumulated in tumor tissue in larger concentrations than in normal ones should be also noted.

In general, redox–active transition–metal complexes capable of catalyzing both formation and consumption of reactive oxygen species (ROS) are of special interest, as first emphasized by M. Vol'pin [8, 9]. Our studies are focused on a specific type of redox–active cobalt complexes, namely those including both tetradentate aliphatic Schiff base and biogeneous or related synthetic nitrogenous base ligands. Presumably, such complexes may be reversibly reduced under hypoxia, giving rise to a catalytic autoxidation process resulting in generation of reactive oxygen species (ROS). On the other hand, a high level of hypoxia just occurs in solid tumors which contain significant regions at low oxygen tensions [10]. We hypothesized that these properties may be exploited for the development of new anticancer agents.

We have synthesized and thoroughly characterized some complexes of the above type, namely those including nicotinamide (nic), isonicotinamide (*i*–nic), nicotinic acid (nic–ac) and some other nitrogenous bases as axial ligands. It is noteworthy that the molecular weights of our complexes do not exceed 620 Da. These values are appropriate for chemotherapeutical agents,

Received: January 8, 2004.
*Correspondence: E–mail: osion@onconet.kiev.ua

since low–molecular drugs (with molecular mass ≤ 500 Da) can be relatively readily delivered into cells and are, *ceteris paribus*, most appropriate for industrial production [11].

These cobalt complexes were shown to produce substantial anticancer effects: inhibition of primary tumor growth and metastases was in the range of 45–80% and 65–99% respectively [12]. Presumably, the mechanisms of these effects reflect their reactivity. Namely, they may be reduced under hypoxic conditions to generate ROS which attack and damage biomolecules, thus retarding tumor growth [13]. However, there have been no quantitative data yet on the selectivity of action of the complexes upon tumor tissues. This study was aimed to test the hypothesis that our cobalt complexes, which are reducible under hypoxia with the generation of ROS, may selectively affect tumor tissue including those with significant hypoxic regions.

MATERIALS AND METHODS

Compounds. Octahedral cobalt(III) complexes containing both the equatorial tetradentate dianionic Schiff base ligand derived from acetylacetone and ethylenediamine, and axial monodentate ligands of the vitamin PP series or their synthetic analogs [14] were tested in the experiments *in vivo*. Compounds were either cationic complexes of the common symbolic formula $[Co(acac_2en)L_2]Br$, where L is nicotinamide (nic) or *iso*nicotinamide (*i–nic*), (AC–30 and AC–40, respectively), or the neutral complex $[Co(acac_2en)(nica)(nica_{-H})]$ (AC–31) including both nicotinic acid (nica) and its anion ($nica_{-H}$) as axial ligands.

Complexes were dissolved in *aqua pro injectionibus* immediately before use and injected intraperitoneally. They were administered at a dose of 12 mg/kg of body weight. This dose was chosen as a therapeutic one in accordance with LD_{50} values of the substances in question.

Tumors. Transplanted mice tumors, namely Lewis lung carcinoma (3LL), melanoma B16, and mammary adenocarcinoma Ca755, were treated in this study. Female mice of the inbred strain C57Bl/6, mean weight 20–25 g, were used. Tumors were transplanted intramuscularly into a leg. The principles and methods of transplantation were conventional. Animals were kept in Makrolon cages bedded with dust–free wood granules, and had free access to a standard diet and tap water. Administration of complexes was performed when tumors were ca. 0.9–1.2 cm^3 in volume. All experiments had been approved by the regional animal ethics committee.

Methods. The concentrations of malondialdehyde in tissue extracts were determined by standard biochemical methods. The rate of DNA strand unwinding which had been proved [15] to be a sensitive measure of DNA damage in living cells was monitored using a fluorimetric technique applicable to different DNA damaging agents and cells from animal organs [15]. Practically, the rate of strand unwinding was determined after the treatment of crude cell lysates with aqueous alkali. ^{31}P NMR spectra (121.5 MHz) of perchloric acid tissue extracts were recorded with a Mercury – 300 BB Spectrometer (Varian, USA) equipped by Sparcs station 4, using a probe tube of 5 mm inner diameter. As a standard substance, methylenediphosphonic acid trisodium salt (Sigma, USA) was used. The Pi/PCr, Pi/βNTP and PME/βNTP ratios were used as the most reliable and frequently applied ^{31}P NMR parameters for estimation of the changes in the tissue bioenergetics and levels of hypoxia [16].

Statistical analysis. Values given in this study are means ± s.e.m. The significance of the differences between the various groups was estimated by Student's test. Differences were considered as significant if p was ≤ 0.05.

RESULTS AND DISCUSSION

Our principal hypothesis is that these cobalt complexes generate ROS in hypoxic zones characteristic of tumor rather than normal tissues. Thus, the maximal damage to biomolecules in the experimental animals upon administration of the complexes should be localized in malignant tissues.

Lipid peroxidation. Levels of lipid peroxidation were estimated by determination of the concentration of malondialdehyde (MDA) as a terminal product of lipid peroxidation. The data thus obtained are presented in Table 1.

Table 1. Malondialdehyde concentrations (nmol/mg tissue) in Lewis lung carcinoma and some normal tissues in tumor–bearing mice upon administration of the cobalt complexes AC–30, AC–40, or AC–31 at a dose of 12 mg/kg

Tissue	Time after complex administration (hours)				
	0 (control)	1	2	6	24
			Complex AC–30		
Tumor	5.9 ± 1.2 n = 15	10.6 ± 2.1* n = 6	17.2 ± 2.7* n = 6	15.2 ± 0.9* n = 5	5.1 ± 0.9 n = 6
Liver	6.2 ± 0.9 n = 15	10.6 ± 5.1 n = 6	5.3 ± 0.7 n = 6	5.5 ± 0.65 n = 5	7.6 ± 0.9 n = 6
Kidney	6.9 ± 0.5 n = 15	17.8 ± 6.4* n = 6	7.45 ± 1.2 n = 6	10.3 ± 3.7 n = 5	7.0 ± 1.8 n = 6
			Complex AC–40		
Tumor	5.9 ± 1.2 n = 15	9.2 ± 1.9* n = 6	11.2 ± 2.2* n = 6	12.3 ± 1.8* n = 5	6.9 ± 1.4 n = 6
Liver	6.2 ± 0.9 n =15	7.8 ± 2.1 n = 6	7.5 ± 1.7 n = 6	6.9 ± 0.55 n = 5	6.4 ± 0.5 n = 6
Kidney	6.9 ± 0.5 n = 15	7.7 ± 2.7 n = 6	8.7 ± 2.3 n = 6	7.5 ± 3.7 n = 5	6.2 ± 1.4 n = 6
			Complex AC–31		
Tumor	5.9 ± 1.2 n = 15	8.15 ± 0.9* n = 7	12.15 ± 1.7* n = 7	9.9 ± 1.2* n = 7	5.85 ± 1.4 n = 4
Liver	6.2 ± 0.9 n = 15	4.2 ± 1.3 n = 7	4.8 ± 1.0 n = 7	5.3 ± 2.0 n = 7	7.8 ± 1.5 n = 4
Kidney	6.9 ± 0.5 n = 15	6.1 ± 0.5* n = 7	8.5 ± 1.5 n = 7	7.6 ± 1.9 n = 7	8.4 ± 1.1 n = 4

* $p < 0.05$ in comparison with control value; n – number of mice.

The administration of complex AC–30 resulted in a 2.9–fold increase of MDA concentration in tumor 2 h after injection accompanied with minor changes of MDA content in liver only. However, the MDA concentration in kidney was increased by a factor of 3.0 1 h after AC–30 injection. In the case of complex AC–40, there was a 1.9–fold increase of MDA content in tumor 2 h after injection without changes of MDA content both in liver and kidney. Further, MDA concentration increased by a factor of 2.1 in tumor 2 h after AC–31 injection, while it did not change in liver and kidney. These results support the suggestion that our complexes are selectively reduced in tumors, initiating a catalytic au–

toxidation process involving generation of ROS. This oxidative stress apparently activated the peroxidation of lipids leading to the formation of MDA.

DNA damage. No significant differences in the rate of DNA unwinding in peripheral white blood cells was found between experimental groups of animals, either treated with i.p. injections of complexes AC–30 and AC–31, or untreated (controls). Only in the animals treated with AC–30, the DNA unwinding somewhat speeded up 2 h after injection of the complex; namely, it became ca. 10% faster compared with that in untreated donor animals.

Further, the rates of unwinding of DNA from tumors of mice administered with AC–30 by means of i.p. injections were compared with those from DNA from tumors from untreated animals. The former measured 2 h after injection proved much faster than the latter, namely by a factor of 3.5 on average (Fig. 1). Then up to 48 h after the injection, the proportion of double–stranded DNA increased, while still remaining below the initial high level. Namely, 2, 24 and 48 h past the injection, it was 33, 55 and 58% respectively, as compared with 81% for untreated tumors. The initial level for determination of the rate of unwinding of DNA strands in tumor cells was taken as 100% at 0 °C during the 30–min period of equilibration with alkali.

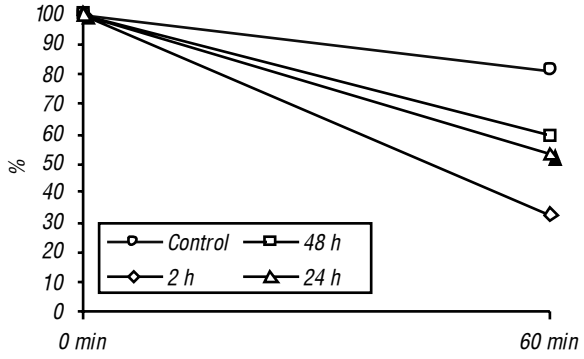

Fig. 1. Relative number of double–strand DNA (%) in Lewis lung carcinoma cells 60 min after incubation in alkali

The changes of DNA unwinding rate in tumor cells of 3LL–bearing mice treated with AC–31 were qualitatively similar to those in the above experiments with AC–30, but less pronounced: 2, 24 and 48 h after injection of the former complex, the proportion of double–stranded DNA was 46, 61 and 65.5%, respectively (controls – 78.1%).

These data demonstrated that cobalt complexes exert a direct effect on the structure of DNA, producing strand breaks in tumor cells. The level of DNA damage evidently depends on the nature of the axial ligands in the complexes.

Tumor bioenergetics. ^{31}P NMR spectra of perchloric acid (PCA) extracts of tumor tissue and muscle of 3LL carcinoma–bearing mice as well as those from healthy controls were recorded in order to monitor the effects of administration of complexes AC–30, AC–40 and AC–31.

In this manner, levels of phosphorus–containing substances in tissues of mice killed at various intervals (2, 6, 24 and 48 h) after injection of the complexes have been measured. The spectra of 3LL carcinoma tissue had a similar profile to that found in the literature, with variations in the relative concentrations of metabolites (Fig. 2).

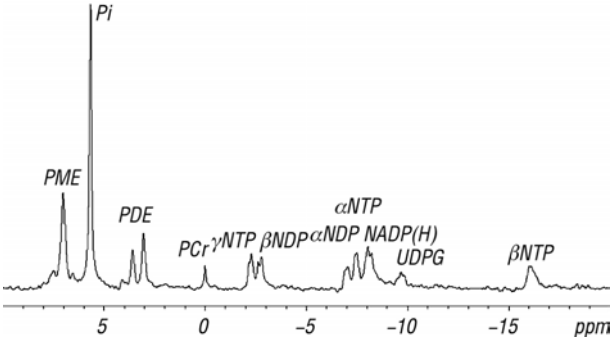

Fig. 2. ^{31}P NMR spectrum of perchloric extract of Lewis lung carcinoma of untreated mice

After administration of complex AC–30, levels of high–energy phosphates in tumor tissue declined significantly 2 h after injection (Fig. 3B). The ratios Pi/PCr, Pi/βNTP and PME/βNTP were significantly increased by this time point: by 5.2–, 4.1– and 3.5–fold, respectively, presenting convincing evidence for an elevated hypoxia level in tumor tissue as well as a significant reduction of the energy status.

These ratios did not completely return to the pre–treatment level 24 h after AC–30 injection (Fig. 3C), being something lower than the initial values (by 17, 22 and 26% respectively) 48 h following complex injection (Fig. 3 D).

In the case of administration of complex AC–40, levels of high–energy phosphates in tumor tissue also declined 2 h after injection. The Pi/PCr, Pi/βNTP and PME/βNTP ratios increased with maximum values at 2 h after injection, by a factor of 3.2, 2.8, and 1.5 respectively. Then the decrease of Pi/βNTP and PME/βNTP ratios (both by a factor of 1.7) and Pi/PCr ratio (by a factor of 1.4) was observed at 6 h after injection relative to the values at the 2 h point. Nevertheless, at 24 h, they were still elevated (by a factor of 1.7, 2.3, and 33% respectively in comparison with the pre–treatment levels). Thus, changes of intensities in the resulting ^{31}P NMR spectra with time deviated somewhat with AC–40 compared to those after administration of AC–30.

After administration of AC–31, levels of high–energy phosphates in tumor tissue also declined 2 h after injection. The ratios Pi/PCr, Pi/βNTP and PME/βNTP increased, but not so markedly as they did in the case of AC–30. At this time point, these ratios were elevated (by 20%, 12%, and 2–fold respectively), and they almost completely returned to the pretreatment level within 24 h after AC–31 injection.

The data obtained suggest that one of the causes of antitumor activity of cobalt complexes is their capacity to reduce the energy status in tumors as well as to enhance the tumor hypoxia which also influences the antitumor activities of these complexes. It may be also concluded that the level of cellular damage inflicted by complexes depends on the nature of their axial ligands.

Examination of ^{31}P NMR spectra of the PCA tumor extracts has shown that the ability of AC–30 to enhance tumor hypoxia is much higher than those of the

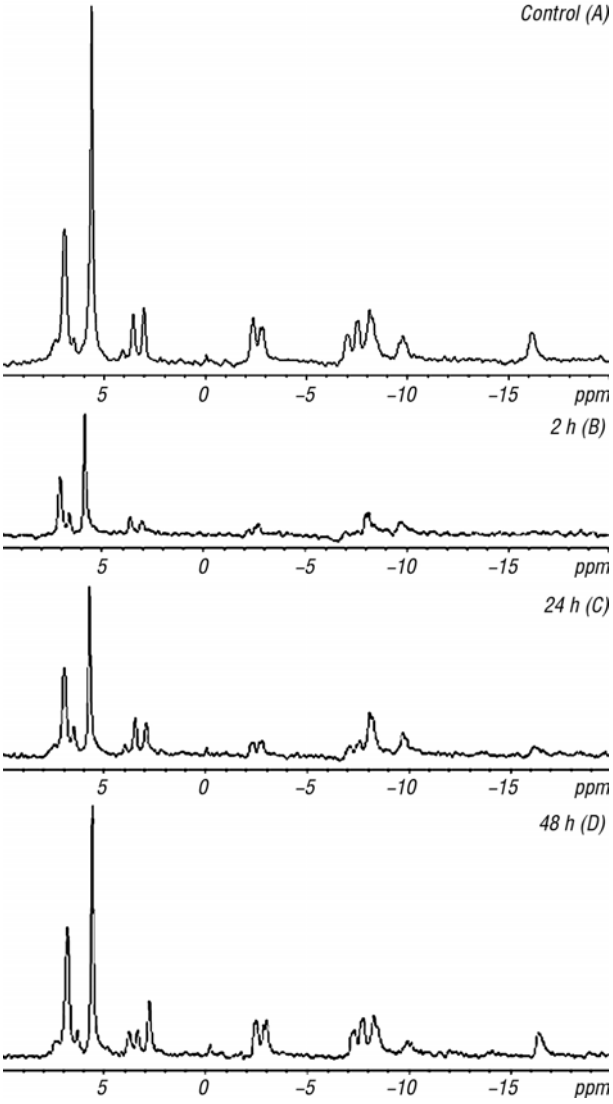

Fig. 3. ^{31}P NMR spectra of perchloric extracts of Lewis lung carcinoma in control and after AC–30 treatment

two other complexes. At the same time, all the complexes induce an essential reduction of tumor 'bioenergetic status'. One can conclude that these peculiarities of the biological effects of the complexes correspond to their antitumor and antimetastatic activities.

Further, evaluation of muscle response to the complexes was also performed after their administration into tumor–bearing mice. Some results thus obtained are presented in Fig. 4. After AC–30 administration, the Pi/PCr, Pi/β–NTP and PME/β–NTP ratios in muscle tissue were not significantly changed: they remained almost stable with marginal changes within the observation period. The Pi/β–NTP and the PME/β–NTP ratios showed some gradual increase up to 24 h following complex administration (43% and 28% respectively), and did not completely return to the base–line value 48 h after injection.

In muscle tissues of tumor–bearing mice, the Pi/PCr, Pi/βNTP and PME/βNTP ratios increased by a factor of 1.4, 1.1 and 1.3 respectively at 2 h after AC–40 injection and then gradually increased 1.7–, 1.4– and 1.6–fold by the 48 h point.

After AC–31 administration, almost the same situation was observed for muscle tissue up to 6 h as it

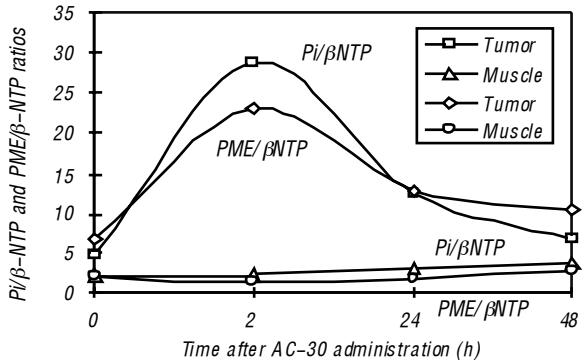

Fig. 4. Pi/βNTP and PME/βNTP in muscle of tumor–bearing mice (3LL) after AC–30 administration in compare to those in tumor

was after AC–30 administration, but then there was a gradual increase of the PME/β–NTP ratio to 37% at 48 h following complex administration.

It is pertinent that similar results were obtained with the Guerin carcinoma in our previous study [17].

The data thus obtained support the assumption that cobalt complexes display some selectivity with respect to tumor tissue and have time–dependent effects on tumor and muscle tissue.

Overall, we conclude that injections of complexes AC–30, AC–40 and AC–31 causes significant reduction of bioenergetic status and enhancement of tumor hypoxia. Similar effects were also observed in muscle tissue, but to a considerably less extent, and they became notable only a long time after complex administration. It is possible that the antitumor efficacy of cobalt complexes results from both the reduction of energy status of tumor tissue and an increase in tumor hypoxia [17].

Conclusion. The outcome of this work as well as results of similar experiments with the Guerin carcinoma in rats provide convincing evidence that the action *in vivo* of these cobalt complexes cause significant changes in metabolism, namely activation of lipid peroxidation, DNA damage and reduction of the bioenergetic status in tumor tissue while practically lacking effects in normal tissues. In general, they reveal a high selectivity of action by the complexes upon tumors and support our principal assumption that it is due to their specific reactivity. Namely, our recent studies both *in vitro* and *in vivo* [14] have shown that such complexes may be reduced in hypoxic regions of malignant tumors with the formation of ROS, viz. superoxide anion. It is noteworthy that its generation was observed as a tumor–selective process.

Finally, all these findings support the feasibility of the development of selective anticancer agents on the basis of such redox–active cobalt complexes.

ACKNOWLEDGEMENT

The study was supported by INTAS (Grant No 00–665). The authors would like to thank Dr. V.M. Mikhailenko, Mrs. T.K. Sergienko, Mrs. N. Okhotnikova, and Ms. S. Zimina for careful technical assistance.

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СЕЛЕКТИВНОСТЬ ДЕЙСТВИЯ РЕДОКС–АКТИВНЫХ КОМПЛЕКСОВ КОБАЛЬТА(III) НА ОПУХОЛЕВУЮ ТКАНЬ

***Цель*: установить степень селективности действия комплексов кобальта на опухолевую ткань. *Материалы и методы*: комплексы кобальта(III) с тетрадентатным основанием Шиффа из ацетилацетона и этилендиамина, содержащие также (в качестве аксиальных лигандов) соединения ряда витамина PP (никотинамид или никотиновую кислоту) или их аналог (изоникотинамид), тестировались в опытах *in vivo*. Исследовали перевивные опухоли мышей, в частности карциному легких Льюис, меланому B16 и аденокарциному молочной железы Ca755. Концентрацию малонового диальдегида в опухоли определяли стандартным биохимическим методом, повреждение ДНК в опухолевых клетках оценивали по скорости раскручивания ДНК, уровень гипоксии и биоэнергетический статус определяли с помощью ^{31}P ЯМР-спектроскопии в перхлорных тканевых экстрактах. *Результаты*: установлено существенное и селективное повышение концентрации малонового диальдегида в опухоли после введения комплексов, что свидетельствует об активации перекисного окисления липидов. Биоэнергетический статус в опухоли селективно подавлялся под влиянием комплексов: через 2 ч после их введения сигналы богатых энергией фосфатов практически отсутствовали. В опухоли увеличивалось количество однонитевых разрывов ДНК, что позволяет предположить прямое повреждающее действие комплексов на молекулу ДНК. Выявлена корреляция между выраженностью отмеченных событий в опухоли и химической природой аксиального лиганда. *Заключение:* комплексы кобальта высокоселективны в отношении опухолевой ткани, в частности активируют процессы перекисного окисления липидов, вызывают однонитевые разрывы ДНК и угнетают биоэнергетику. Высказано предположение, что селективное по отношению к опухоли действие комплексов обусловлено особенностями микроокружения опухолевых клеток, в частности выраженной внутриопухолевой гипоксией.**

***Ключевые слова*: редокс-активные комплексы кобальта, гипоксия опухоли, селективность, активные формы кислорода.**