

Their reactions with platinum(II) and palladium(II) halides will be reported and discussed, together with the preliminary cytotoxicity data. Except for $M(\text{HDdte})_2$ and unlike the corresponding $M(\text{DEdte})_2$, where DEdte is the diethyldithiocarbamate anion, M is Pt or Pd, $M(\text{TAdtc})_2$ and $M(\text{MAdtc})_2$ are very soluble in several organic solvents, so that these compounds are promising for future biological studies.

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REFERENCES

- [1] P.T. DALEY-YATES, D.C.H. MCBRIEN, *Biochem. Pharmacol.*, **33**, 3063 (1984).
- [2] R.F. BORCH, D.L. BODENNER, J.C. KATZ in M.P. HACKER, E.B. DOUPLE, I.H. KRAKOFF (eds.), «Platinum Coordination Complexes in Cancer Chemotherapy», Martinus Nijhoff Publ., Boston, 1984, p. 256.
- [3] G. RENOUX, *J. Pharmacol.*, **13**, suppl. I, 95 (1982).
- [4] G. FARAGLIA, L. SINDELLARI, L. TRINCIA, A. FURLANI, V. SCARCIA, *Inorg. Chim. Acta*, in press.



PS6.16 — TH

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THE ONCOGENE OF MURINE SARCOMA VIRUS V-Ki-ras MAY ARISE AS A RESULT OF CHEMICAL ACTION ON THE PROTOONCOGENE c-ras

The processes of nucleotide transition and transversion leading to point mutations in DNA play a certain role in the malignant transformation. The cause of such transformations may consist either

in bivalent transition metals, *e.g.* $G \cdot \text{Me}^{2+} \rightarrow A$ (where G is guanine and A is Adenine) as E.L. ANDRONIKASHVILI and N.G. ESIPOVA [1] have shown, or in the methylation processes considered in detail by G. KLOPMAN and A. RAY [2] from the view-point of quantum biochemistry. Thus, for instance, at CH_3 group binding with guanine 06 the electronic structure of this nucleotide becomes similar to that of adenine, whereas thymine alkylation in 04 transforms it into cytosine-like state.

On the other hand, as a result of the investigations carried out by R. WEINBERG [3], M. BARBACID [4] and their collaborators, it has become evident that the point mutation in coding GGC triplet occupying the 12th position in the normal cellular gene c-ras (which is also called protooncogene) is characteristic of human bladder carcinoma (of chemical origin). This mutation transforms GGC triplet into GTC triplet.

However, the same 12th triplet of protooncogene undergoing $\text{GGC} \rightarrow \text{AGC}$ mutation becomes a characteristic feature of Kirsten viral murine sarcoma. The respective oncogene is called V-Ki-ras. However, in order to cause $G \rightarrow A$ transition, as it has been shown in refs. [1] and [2], the interference of a certain chemical agent is sufficient. Such an agent may be both a bivalent transition metal ion and a methylic group CH_3 .

Thus, in order to cause the formation of oncogene typical of murine sarcoma virus from a normal cellular gene of c-ras type, it is sufficient that the first guanine of the 12th GGC triplet would trap a bivalent transition metal ion or that alkylguanine would arise instead of guanine.

The oncogene of virus causing malignant diseases formed as a result of chemical action will act subsequently in accordance with viro-genetic theory. It should be emphasized that other mutations of the GGC triplet under consideration, as well as those of coding triplets of other types, being characteristic of one or another neoplasia, may have no connection with viral transformation.

Clearly, at the present stage of carcinogenesis theory development, we have no reasons to make a sharp distinction between viro-genetic and chemical theories.

REFERENCES

- [1] E.L. ANDRONIKASHVILI, N.G. ESIPOVA, *J. Mol. Catal.*, **23**, 195 (1984).
- [2] G. KLOPMAN, A. RAY, *Cancer Biochem. Biophys.*, **6**, 31-35 (1982).
- [3] C.J. TABIN, S.M. BRADLEY, C.J. BARGMAN, R.A. WEINBERG, *Nature (London)*, **300**, 143-149 (1982).
- [4] E.P. REDDY, R.K. REYNOLDS, E. SANTOS, M. BARBACID, *Nature (London)*, **300**, 149-152 (1982).



PS6.17 — MO

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TUMOR LOCALIZING METAL COMPLEXES

We reported [1] that the radioactivity was concentrated in tumor tissues in experimental animals a few hours after the administration of the complexes of ethylenediamine-*N,N*-diacetic acid (EDDA) and related chelating agents with ^{99m}Tc . The tumor tissues were clearly visualized in scintigrams [2].

Complexes of EDDA with other radioactive metal ions and ^3H -labeled EDDA were prepared and the biodistribution of the radioactivity in mice bearing Ehrlich tumor was studied. The tumor/blood and tumor/muscle ratios of the radioactivity indicated that ^{57}Co EDDA was concentrated in the tumor tissues. The higher affinity for the tumor was noted with $\mu\text{-oxo } ^{57}\text{Co}$ EDDA, which was prepared by treatment of ^{57}Co EDDA with hydrogen peroxide. The ^{51}Cr , ^{59}Fe , ^{64}Cu and ^{67}Ga complexes of EDDA as well as ^3H -labeled EDDA were not concentrated in the tumor.

The tumor localizing EDDA complexes (^{99m}Tc EDDA and $\mu\text{-oxo } ^{57}\text{Co}$ EDDA) and related radioactive compounds, which are not tumor localizing, were injected intravenously to rats. The compounds studied were $\text{Na}^{99m}\text{TcO}_4$, $^{57}\text{CoCl}_2$, and the complexes of *N'*-acetythylenediamine-*N,N*-diacetic acid (AcEDDA) with ^{99m}Tc and ^{57}Co . Hepalinized blood was collected 1 h after the injection and was analyzed by density gradient centrifugation and dialysis.

Most of the radioactivity was present in blood plasma and cellular fractions contained less than 10% of the radioactivity. Results of dialysis of the blood against physiological saline were significantly different between the tumor localizing and not localizing complexes. Most of the radioactivity was dialyzable in the blood of rats administered with $^{99m}\text{TcO}_4^-$ and more than 80% was dialyzed in 24 h in those of the EDDA complexes. In those of the other radioactive compounds, more than 60% radioactivity was remaining undialyzed indicating that the radioactivity was firmly bound to plasma proteins.

The radioactive compounds were administered to mice bearing Ehrlich tumor. The tumor tissues were removed at selected times, homogenized, separated into nuclear, mitochondrial, microsomal, and supernatant fractions by centrifugation, and measured the radioactivity of the fractions. The results showed that the EDDA complexes were concentrated in the nuclear fraction, whereas the other compounds in the supernatant fraction. From the results above mentioned, the following conclusions may be drawn on the tumor localizing EDDA complexes. The EDDA complexes of ^{99m}Tc and ^{57}Co were not firmly bound to plasma proteins *in vivo*. Hence they were rapidly transferred into tumor tissues and rapidly cleared through kidneys from blood. Relatively high radioactivity in tumor tissues and low radioactivity in blood should give clear scintigrams of the tumor tissues.

REFERENCES

- [1] Y. MATSUSHIMA, Y. KARUBE, presented at 1st ICBIC, *Inorg. Chim. Acta*, **79**, 285 (1983).
- [2] Y. KARUBE *et al.*, *Chem. Pharm. Bull.*, **29**, 2385 (1981); **30**, 2529 (1982); **31**, 3242 (1983); **32**, 4049 (1984).