HOW THE MULTIFUNCTIONAL NANOCARRIER MAKES THE MEDICINE «SMART»?

R. Stoika

Institute of Cell Biology, NAS of Ukraine, Lviv, Ukraine, stoika@cellbiol.lviv.ua

Key words: nanoscale platform, anti-cancer drugs, nanocarrier, on Fullerene C60

The principal problems in pharmacology are non-addressed action of medicines causing negative side effects in the organism and rapid development of drug resistance in treated patients. Here we present examples how drug encapsulation in the polymeric or mineral nanoscale platform can enhance its treatment effect, improve its targeting in the organism, as well as provide the drug with ability to circumvent drug-resistance mechanisms. Thus, such encapsulation makes the drug "smarter" during its action.

Different anti-cancer drugs (Doxorubicin, Cisplatin, Ruthenium-containing drug KP-1019, Landomycin A, novel 4-tiazolodininone derivatives) were conjugated with either poly (VEP-GMA)-graft-PEG additionally functionalized with phospholipid or conjugated with Fulleren C60. The drugs were applied in native and nanocarrier-immobilized forms for treatment of mammalian tumor cells of various tissue origin and with different mechanisms of resistance to anticancer drugs.

Immobilization of Doxorubicin and KP-1019 on a new polymeric-phospholipidic hybrid delivery system distinctly enhanced the accumulation and activity of these drugs in all tested tumor cell lines including several drug-resistant lines. The resistance levels against Doxorubicin were reduced 6- to 22-fold. The new nanocarriers were shown to rapidly (within 10 min) and effectively transport Doxorubicin into drug-resistant as well as drug-sensitive tumor cells. The treatment with new Doxorubicin-containing nanocarriers resulted in effective cell cycle arrest in G2/M phase and ROS-induced cell death. In both *in vivo* tumor models – murine NK/Ly lymphoma and murine L1210 leukemia – Doxorubicin delivery by the new nanoformulation resulted in 100% cured animals already at low concentrations (0.1 mg/kg), while the native Dox solely extended a survival time. Thus, polymeric nanocarriers functionalized with phospholipids and PEG enhance the efficacy and reduce the toxicity of Doxorubicin.

In another set of experiments, Doxorubicin or Cisplatin (CDDP) were immobilized on Fullerene C60 that enhanced an ability of these anticancer drugs to circumvent resistance of tumor cells to chemotherapy *in vitro.* Cytotoxic activity of CDDP-C60 nano-complex towards different lines of drug-resistant tumor cells was 1.5-2.0 times higher than that of native CDDP. In parallel, an enhanced uptake of this drug and double induction of apoptosis in target tumor cells were observed. The anticancer effect of CDDP-C60 nano-complex was confirmed in tumor-bearing mice.

We also functionalized the developed polymeric nanocarriers with specific antibody or lectin in order to improve their cell targeting properties.

Acknowledgements: Zaichenko O., Mitina N., Ryabtseva A., Myahkota L., Hevus O., Senkiv Yu., Heffeter P., Berger W., Boiko N., Klyuchivska O., Finiuk N., Lootsik M., Panchuk R., Skorokhyd N., Lehka L., Prylutskyy Yu., Prylutska S., Evstigneev M., Potebnya G., Skivka L., Didenko G., Ritter U., Scharff P., Kobylinska L., Havrylyuk R., Kamynsky D., Lesyk R., Zimenkovsky B.