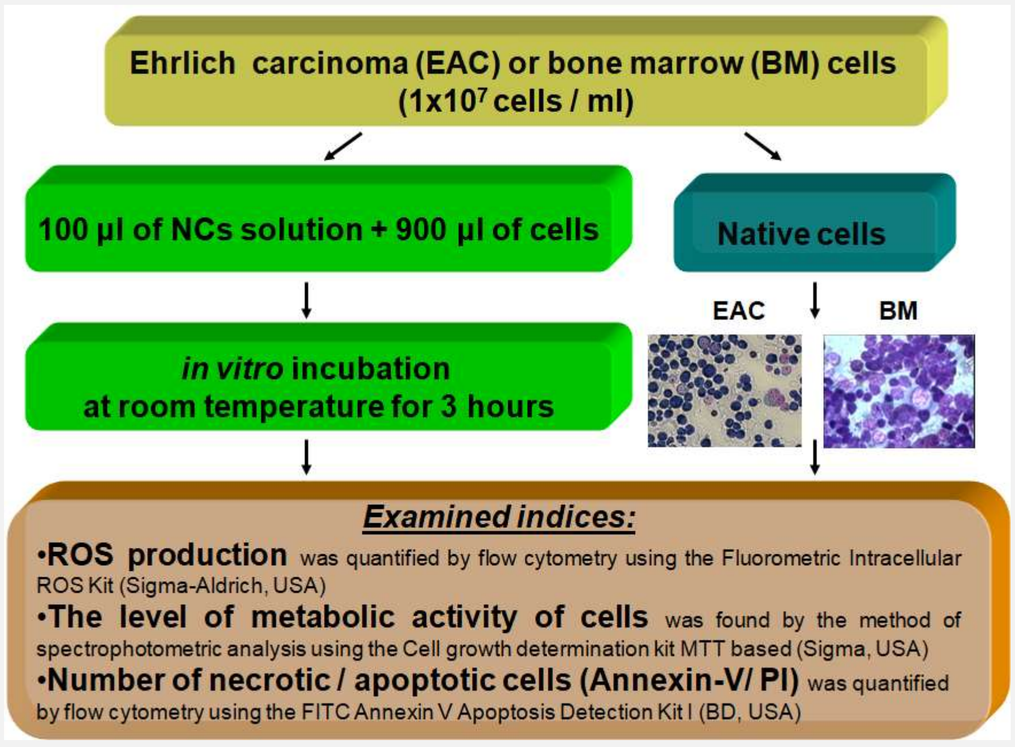
Formation of reactive oxygen species as one of the triggers of antitumor action of nanocomplexes

Anatoliy Goltsev, Mykola Bondarovych, Natalia Babenko, Yuliia Gaevska, Tetiana Dubrava, Maxym Ostankov

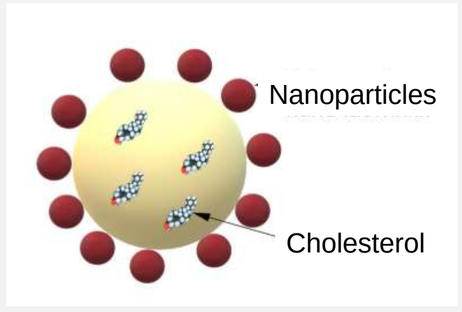
Cryopathophysiology and Immunology Department,
Institute for Problems of Cryobiology & Cryomedicine of the National Academy of Sciences of Ukraine. Pereyaslavska Str, 23, Kharkiv 61016, Ukraine.
E-mail:cryopato@gmail.com

Experimental study of the antitumor effects of nanocomplexes (NCs), consisting of nanoparticles of $GdYVO_4:Eu^{3+}$ and cholesterol, indicates the feasibility of their use in oncology practice. Using *in vivo* research model of Ehrlich carcinoma, the possibility of using NCs for the purpose of simultaneous targeting of cancer stem cells (CSCs) and inhibition of their function was substantiated. This can nonspecifically affect function of different cell structures, that makes it relevant to study the biosafety of vanadium nano-sized compounds against hematopoietic cells of the recipient, especially stem cells, which have common features of their functioning with CSCs.
The aim of the research was to study the possible mechanisms antitumor action of NCs

Experimental Design

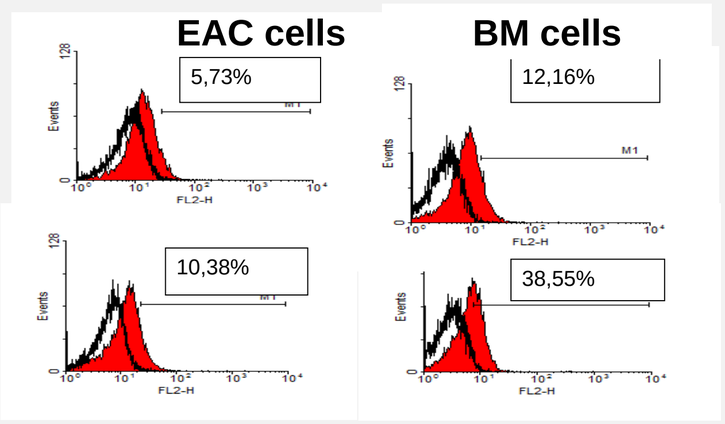


Schematic representation of NC

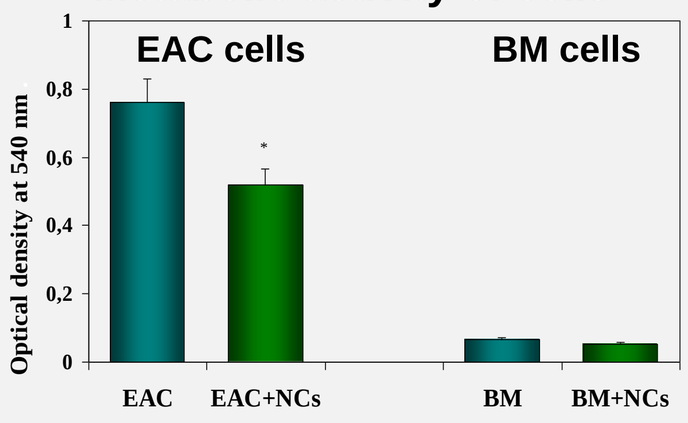


The nanocomplex, synthesized first at the Institute for Scintillation Materials of the National Academy of Sciences of Ukraine, is the product of aqueous dispersion of cholesterol (0,55 g/l) and NPs (1.3 g/l) of rare earth orthovanadates of $GdYVO_4:Eu^{3+}$ composition

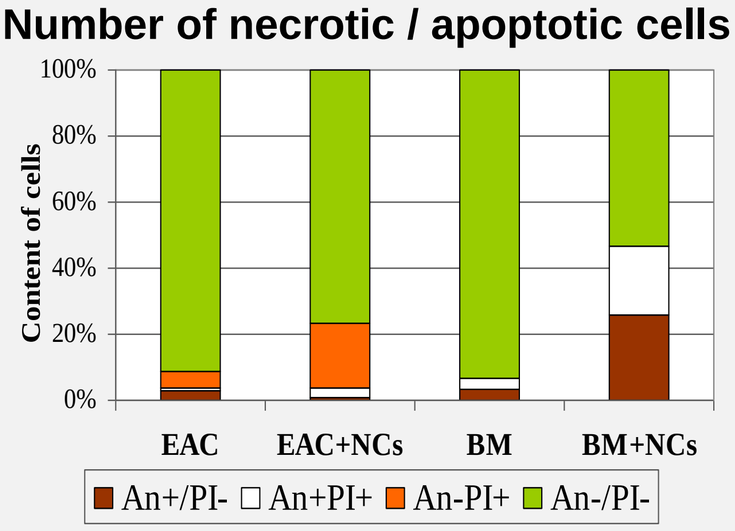
ROS production of cells



Metabolic activity of cells



Number of necrotic / apoptotic cells



Results

The EAC cells before NCs treatment were found to have a basal level of ROS production at 12.16±0.93%, which was twice higher than in BM cells. Treatment with NCs increased the number of ROS-positive cells in BM by 1.8 times and in EAC by more than 3 times compared to the corresponding basal levels, which was a prerequisite for a deeper disorder of their functional state.

According to the MTT test results, it was found that NCs reduced by 32% the metabolic activity of EAC cells. The inhibitory effect of NCs on the metabolism of BM cells was less significant, i.e. the NCs reduced the activity of mitochondrial respiration by 18.5%. Under the influence of NCs, the inhibition rate of metabolic activity of EAC cells by MTT test was almost 10 times greater than that of BM cells, that is a reflection of inhibition of NADP-H-dependent oxidoreductase enzymes of mitochondria.

This led to a significant decrease (by 15%) in the number of living (An^-/PI^-) EAC cells. Predominantly, the death of tumor cells after incubation with NCs occurred due to necrosis (An^-PI^+). Nanocomplexes were able to increase in the number of BM cells in the state of early (An^+/PI^-) and late apoptosis (An+/PI+).

Conclusions

Our results suggested that one of the possible ways of antitumor action of NCs is generation of ROS with subsequent damage to mitochondrial function or induction of cell death by apoptosis / necrosis. Further research will be focused on testing the approaches to increase an antitumor activity of the used nanocomplexes.

Acknowledgements

The authors of the paper express their sincere gratitude to senior researcher at the Department of Nanostructured Materials of the Institute for Scintillation Materials of the NASU Ph.D. Volodimir Klochkov for the synthesis of nanocomplexes