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VIII ВСЕРОССИЙСКАЯ НАУЧНО-ПРАКТИЧЕСКАЯ КОНФЕРЕНЦИЯ С МЕЖДУНАРОДНЫМ УЧАСТИЕМ, ПОСВЯЩЕННАЯ 50-ЛЕТИЮ ОСНОВАНИЯ ИНСТИТУТА ХИМИИ НЕФТИ

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ANTICANCER ACTIVITY OF CRUMPLED ALUMINUM NANOSHEETS THROUGH DISRUPTION OF ION BALANCE IN TUMOR MICROENVIRONMENT

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Despite the progress in medicinal chemistry for cancer treatment, chemotherapy is still a major challenge for patients and doctors. Among newly developed biomedical strategies, nanoparticles have been widely exploited in cancer therapy because of their unique physical and chemical properties. One of the newly emerging areas for potential nanoparticle applications in cancer therapy is based on the fact that cancer cells are particularly sensitive to the changes in intracellular and extracellular ion concentrations[1]. Therefore, nanostructures of inorganic materials that affect ion concentrations due to their surface charge and/or adsorption properties[2] could represent a novel strategy for anticancer therapy. In this respect, the nanostructured boehmite form of aluminum hydroxide seems especially attractive due to its unique combination of an extremely large specific surface area and positive surface charge[3]. In addition, Al hydroxide is approved for clinical applications and has been used as a human vaccine adjuvant over six decades, with a demonstrated safety profile[4].

We have shown that Al hydroxide, a well-studied antacid agent and selective adsorbent for many chemicals[5], when synthesized in the form of crumpled and radially assembled nanosheets, causes tumor growth inhibition and cell apoptosis due to a significant ion imbalance in the tumor microenvironment (see Fig.1).

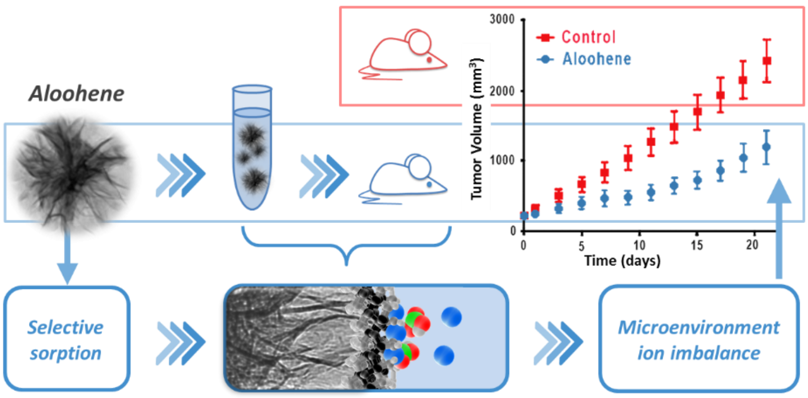

Fig. 1. The principle of tumor treatment strategy through dysregulation of ion balance in the tumor microenvironment using a nanostructured boehmite form of aluminum hydroxide

Al nanoparticles were produced by the electric explosion of Al wires resulted in crumpled nanosheets with the lateral size 400 nm or less and the thickness of 2-5 nm. The synthesized agglomerates of radially assembled crumpled AlOOH nanosheets have been termed Aloohene, referring to its chemical formula AlOOH. Aloohene has a high specific surface area of 284 $m^2 \cdot g^{-1}$ with the width of the slit-shape pores between the crumpled nanosheets 4–19 nm.

The unique anticancer properties of AlOOH nanomaterial were demonstrated on three different cancer cells resulting in 30-37 % decrease in proliferation in all tested cell lines. Moreover, it was shown that pretreatment of PyMT breast cancer cells with Aloohene significantly enhanced the cytotoxicity of the anticancer drug doxorubicin demonstrating the synergistic effect, as confirmed by the method of isoboles based on the concept of dose equivalence. Furthermore, the antitumor effect of Aloohene administered *in vivo* has been shown on two different mouse tumor models demonstrating the compound versatility. The intratumoral injections of Aloohene resulted in a significant reduction of tumor growth as compared to the non-treated mice[6]. Finally, using the direct molecular dynamic stimulation we have confirmed that Aloohene can alter ion concentration in the perimembranous space and thereby affect ion transport, tumor cell nutrition, and vital cellular functions thus providing a plausible explanation for the anticancer effect of this type of nanomaterials.

In summary, our study demonstrates that nanoparticle-based systems capable of disturbing tumor microenvironment extracellular ion balance can represent a novel type of cancer treatment strategy that should be further explored.

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