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METABOLIC ANTICANCER THERAPY BASED ON ARGININE DEPRIVATION: DEVELOPMENT OF THE COMBINATIONAL MODALITIES

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There are several examples of metabolic anticancer therapies based on a single amino acid deprivation (i.e. asparagine, methionine, arginine) that exploit elevated sensitivity of malignant cells to the lack of corresponding amino acids. New progress has been achieved in recombinant production of a number of amino acid- degrading enzymes that can be potentially applicable in humans.

Despite of the recent significant progress in developing arginine-deprivation therapy, mainly in *in vitro* research, to bring it into viable clinical use, several problems have to be addressed. Initial clinical trials with recombinant arginine-degrading enzymes demonstrated such a monotherapy as considerably efficient in controlling proliferation of many highly aggressive tumors auxotrophic for arginine, but less efficient, than had been originally expected, as a curative approach Therefore, new rationally designed combined modalities are expected to increase therapeutic efficacy of arginine deprivation therapy. For this, tumor-specific molecular mechanisms of cells' response to single amino acid starvation and markers of sensitivity to arginine deprivation in different tumor entities have to be identified.

In the Department of cell signaling at Institute of Cell Biology NAS of Ukraine we have recently established on various cell models that such therapeutic adjuvants as inhibitors of autophagic and proteasomal protein degradation, certain amino acid analogues (such as canavanine of plant origin), nitric oxide donors and molecules targeting cells cytoskeleton specifically elevated antiproliferative effects evoked by arginine deprivation. We have recently described that one of the critical cellular responses to single amino acid starvation is mediated by endoplasmic reticulum stress and resulting unfolded protein response mechanisms. In collaboration with Prof. Jolanta Redowicz (Nencki institute of experimental biology PAN, Warsaw, Poland) we observed for the first time that arginine deprivation specifically leads to transient actin cytoskeleton remodeling and impairment of cells metastatic properties. In addition, in collaboration with Prof. Leoni Kunz-Schughart (Oncoray, Technical University Dresden, Germany) it was demonstrated that arginine deprivation, especially in combination with antimetabolite canavanine, leads to profound radiosensitization of tumor cells. Future translational research and animal studies should reveal whether the mentioned combinatory approaches maintain their potential *in vivo*.