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The dysfunction of cGMP-activated Na^+/Ca^{2+} exchange controlling cell hydration is a primary mechanism for carcinogenesis

Overhydration of cells is a hallmark for early detection of cancer. However, the nature of the metabolic mechanism, the dysfunction of which leads to decontrolling of cell hydration and generation of Warburg phenomena in cancer cells, has not been elucidated yet. Na^+/K^+-ATPase, having a central role in metabolic regulation of cell hydration, has three catalytic isoforms with different affinities to ouabain and functional activities. Among these isoforms, the α3 isoform, with the highest affinity to ouabain, isn't involved in ion-transporting process and has an intracellular signaling function. It is known that α3 isoforms of Na^+/K^+-ATPase, which are absent in non-excitable cells of healthy animals, are highly expressed in cancerous cells. Based on this, the expression of these isoforms is considered as one of the early hallmarks for carcinogenesis. However, by our previous work it has been shown that all 3 isoforms are present both in tumor and non-excitable tissues of mice carrying sarcoma-180. It has also been shown that α3 isoform, which is absent in non-excitable cells of healthy animals, appears in non-cancerous tissues of women with breast cancer, as well as in all non-excitable tissues of mice carrying sarcoma-180 tumor. Moreover, it has also been shown that this expression of α3 isoform is accompanied by cell hydration. Based on these data, it has been hypothesized that the dysfunction of intracellular signaling system controlling cell hydration could serve as a primary mechanism for carcinogenesis. To check this hypothesis, in non-excitable tissues of healthy and sarcoma-180 carrying mice (including tumor tissues), dose-dependent ouabain effects on Na^+/K^+-pump activity, cell hydration, intracellular cyclic nucleotides (cGMP and cAMP), glycolysis rate (lactate concentration in blood and lactate dehydrogenase activity), membrane permeability for protons, Na^+/H^+, Na^+/Ca^{2+} exchange and cell proliferation by means of electrophysiological, isotope, immunoassay and microscopic methods were studied. These studies have brought us to conclusion that the dysfunction of α3 isoform-dependent cGMP-activated Na^+/Ca^{2+} exchange in forward mode, which controls Na^+/K^+-pump activity, cell hydration, membrane permeability for Na^+ and Ca^{2+}, glycolysis activity and cell proliferation, is a primary mechanism for generation of cell overhydration and Warburg phenomena leading to carcinogenesis. Therefore, α3 isoform-dependent cGMP-activated Na^+/Ca^{2+} exchange in forward mode has been suggested as a novel therapeutic target for early stage of carcinogenesis.

Speaker Biography

Vagharsh Khachikyan has received his PhD in Cancer Therapy at Yerevan State Medical University. Currently, he is a Physician at National Center of Oncology named after V A Fanarjyan and a Senior Scientist and Lecturer at UNESCO Chair in Life Sciences at Life Sciences International Postgraduate Educational Center. He also conducts lectures on oncology at UNESCO Chair in Life Sciences. His research includes the study of the dysfunction of intracellular signaling system responsible for cancer generation. He has participated in many international trainings and conferences.

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