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ASSESSMENT OF HUMAN ENTEROVIRUSES ONCOLYTIC EFFICIENCY IN TUMOR CELLS IN PRESENCE OF GLICOLITC STRESS

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There are a lot of evidence that viral infection alters host cell metabolism, the mechanisms and consequences of virus-induced metabolic reprogramming barely understood. Viruses clearly rely on host cell machinery to replicate themselves - they promote anabolic processes for generation of macromolecules required for virion replication. Therefore, viral infection triggers metabolic alteration in infected cells to facilitate optimal virus production. Metabolic changes induced by virus infection often mirror metabolic alteration observe in cancer cells, such as upregulation of nutrient consumption and anabolism to support rapid cell growth. Cancer cells and virus-infected cells commonly both exhibit the Warburg effect: increased glycolytic metabolism in the presence of adequate oxygen for oxidative phosphorylation, to supply reducing equivalents and precursors for macromolecule biosynthesis. Oncolytic viruses are not an exception, they also promote alteration in host cell, but they have tropism to cancer cells over normal cells. Precise mechanism for this selectivity is not well studied. However, combination of metabolic drugs approved by FDA and oncolytic viruses could be an effective alternative to viral or metabolic drugs monotherapy.

To test a possible interaction between glucose metabolism and viral oncolysis we assessed sensitivity of cancer cell lines to a panel of human enteroviruses, which ones are effective oncolytic agents with proved clinical efficiency, in presence of glycolytic stress.

In our study we tested a wide panel of viruses, included: poliovirus vaccine strains (PV1, PV2, PV3 -Sabin strains), Coxsackievirus B3(non-canonical strain), Coxsackievirus B4(non-canonical strain), Coxsackievirus B5(non-canonical strain, living enterovirus vaccine 14), Coxsackievir B6 (Schmidt) , Coxsackievirus A7 (non-canonical strain), Coxsackievirus A7 (Parker), CVA21(non-canonical strain), ECHO-1 (non-canonical strain, Living enterovirus vaccine 4), ECHO1 Farouk, ECHO7 (non-canonical strain, living enterovirus vaccine 7), ECHO7 (Rigvir), ECHO12 (non-canonical strain), ECHO12 (Travis), Enteroviruses 75, ECHO-11(non-canonical strain) and ECHO - 30(non-canonical strain), in presence of 2-deoxy-D-glucose (2DG), as a inducer of glycolytic stress, in different murine cell lines: 4T1, B16, CT2A, CT26, GL261.

Our result showed that cells treated with 2DG simultaneously with infection demonstrated enhanced sensitivity to some of tested viruses. CT26 and B16 were not sensitive to any of human enteroviruses, however, addition of 2DG sensibilize CT26 in vitro to CVA7 and ECHO1 viruses. For CT2A cell line ECHO11, ECHO30 and CVB5 has shown oncolytic effect. As for 4T1 addition of 2DG increased sensitivity to CVB3 and CVB5, making it as sensitive as human tumor cell lines.

This investigation allows us to examinate hypothesis about synergic effects of oncolytic viruses and metabolic stress inducing agents (such as 2DG) in vivo, to developped improved therapeutic schemes based on virotherapy.

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