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Antineoplastic drug NSC631570 inhibits C6 glioma growth in rats through the re-education of tumor-associated microglia

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Glioblastoma (GB) is one of the most devastating and fatal tumors. Therapeutic approaches targeting tumor cells have failed. GB is heavily infiltrated with myeloid cells that are collectively referred to as glioma-associated microglia/macrophages or GAM. GAM acquires the alternative, pro-invasive phenotype and creates favorable conditions for disease progression. GAM re-education seems to be an attractive therapeutic approach to GM treatment. NSC631570 is an anticancer agent that influences phagocyte migration and functional polarization. This study was aimed to investigate the effect of NSC631570 on C6 glioma growth in rats and microglia metabolic profile *in vitro* and *in vivo*. For tumor-associated hypoxia induction experiments, the rat microglial cells were treated under either normoxia (21% O2) or hypoxia (3% O2) for 48 hours *in vitro*. Intracranial drug delivery device was developed for the local treatment of glioma-bearing rats with NSC631570. Tumor-bearing animals received seven intracranial injections of the drug at 3 days interval starting from the second day after C6 cell transplantation. NSC631570 re-polarized hypoxic microglia to pro-inflammatory metabolic profile *in vitro*. The treatment of tumor-bearing rats with NSC631570 was associated with prolongation of their life by 18%. This effect was accompanied by the increase in the number of phagocytizing $CD14^+$ cells in the microglia fraction without the alteration in their endocytosis intensity. The frequency of $CD206^+$ cells was moderately increased in the fraction of both $CD14^+$ and CD14-microglial cells. Oxidative metabolism of GAM was moderately down-regulated by the drug. Intracranial introduction of the preparation was associated with the sharp increase of NO generation by microglial cells. Locally introduced NSC631570 can re-educate GAM. This repolarizing effect is associated with moderate tumor growth inhibition and might be considered as an important part of the mechanism of tumor-inhibiting action of the drug.

Biography

Larysa Skivka has completed her PhD from RE Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, NAS of Ukraine and Postdoctoral studies from Taras Shevchenko National University of Kyiv. Currently she is a Professor of the Educational and Scientific Centre, Institute of Biology and Medicine of Taras Shevchenko National University of Kyiv, Ukraine, Head of the Department of Microbiology and Immunology. Her area of scientific activity includes immunomodulation as a component of adjuvant cancer therapy, functional polarization of phagocytes in the pathogenesis of inflammatory diseases.

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