ABSTRACT

Antioxid Redox Signal. 2022 Feb 15. doi: 10.1089/ars.2021.0089. Online ahead of print.

Glioblastoma invasiveness and collagen secretion are enhanced by vitamin C.

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AIMS: Glioblastoma is one of the most aggressive brain tumors. These tumors modify their metabolism, increasing the expression of glucose transporters, GLUTs, which incorporate glucose and the oxidized form of vitamin C, dehydroascorbic acid (DHA). We hypothesized that glioblastoma cells preferentially take up DHA, which is intracellularly reduced and compartmentalized into the endoplasmic reticulum (ER), promoting collagen biosynthesis and an aggressive phenotype.

RESULTS: Our results showed that glioblastoma cells take up DHA using GLUT1, while GLUT3 and sodium-dependent vitamin C transporter 2 (SVCT2), are preferably intracellular. Using a baculoviral system and reticulum-enriched extracts, we determined that SVCT2 is mainly located in the ER and corresponds to a short isoform. AA was compartmentalized, stimulating collagen IV secretion and increasing in vitro and in situ cell migration. Finally, orthotopic xenografts induced in immunocompetent guinea pigs showed that vitamin C deficiency retained collagen, reduced blood vessel invasion, and affected glomeruloid vasculature formation, all pathological conditions associated with malignancy.

Innovation and conclusion: We propose a functional role for vitamin C in glioblastoma development and progression. Vitamin C is incorporated into the ER of glioblastoma cells, where it favors the synthesis of collagen, thus impacting tumor development. Collagen secreted by tumor cells favors the formation of the glomeruloid vasculature and enhances perivascular invasion.

DOI: 10.1089/ars.2021.0089
PMID: 35166128