ABL kinase inhibitors regulate SLC7A11 expression and may treat brain tumors

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Value Proposition

The Abl kinases, Abl1 and Abl2, are a family of non-receptor tyrosine kinases that regulate a wide variety of cellular processes during development and normal homeostasis, but can have deleterious effects on cell survival, proliferation, and cell-cell junction adhesion upon their upregulation following inflammation, tumorigenesis, and oxidative stress. Emerging studies have shown a role for the ABL family kinases, ABL1 and ABL2, in the progression of solid tumors and metastasis. Recent work has also shown that ABL kinases promote neurodegeneration, and that treatment with ABL kinase inhibitors improves astrocytic and synaptic function and reverses cognitive and motor decline in preclinical mouse models. This invention describes a novel novel regulatory mechanism that demonstrates Abl kinase control of SLC7A11 expression, a finding that could be used to treat brain cancers to prevent neuron cell death.

Technology

The inventors discovered a previously unknown role for Abelson (Abl) kinases. Specifically, global transcriptome analysis in lung cancer revealed that SLC7A11 is one of the top differentially regulated genes in Abl-inhibited cells. The Abl inhibitor was GNF5, an inhibitor currently in clinical trials. SLC7A11 regulates glutamate export from the cell. Increased glutamate export can be detrimental to surrounding cells. In particular, neurons undergo glutamate excitotoxicity, a pathway of cell death more commonly associated with stroke and neurodegenerative disease. Glutamate cytotoxicity caused by upregulation of SLC7A11 has been shown to promote glioma growth (by others). Of interest, ABL2 and SLC7A11 expression are both highest in human brain tissue. Thus, inhibitors of Abl kinases could be used to treat brain cancers to prevent neuron cell death.

Advantages

There are currently no FDA-approved treatments for preventing neuron cell death in brain cancers, an area with high-unmet need. This invention could lead to a first in class therapy for such treatment.

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Publications

- A TAZ-AXL-ABL2 Feed-Forward Signaling Axis Promotes Lung Adenocarcinoma Brain Metastasis (Cell Reports, 2019)